Kinetic assumptions in Boolean networks: a case for buffering

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BIOSS seminar

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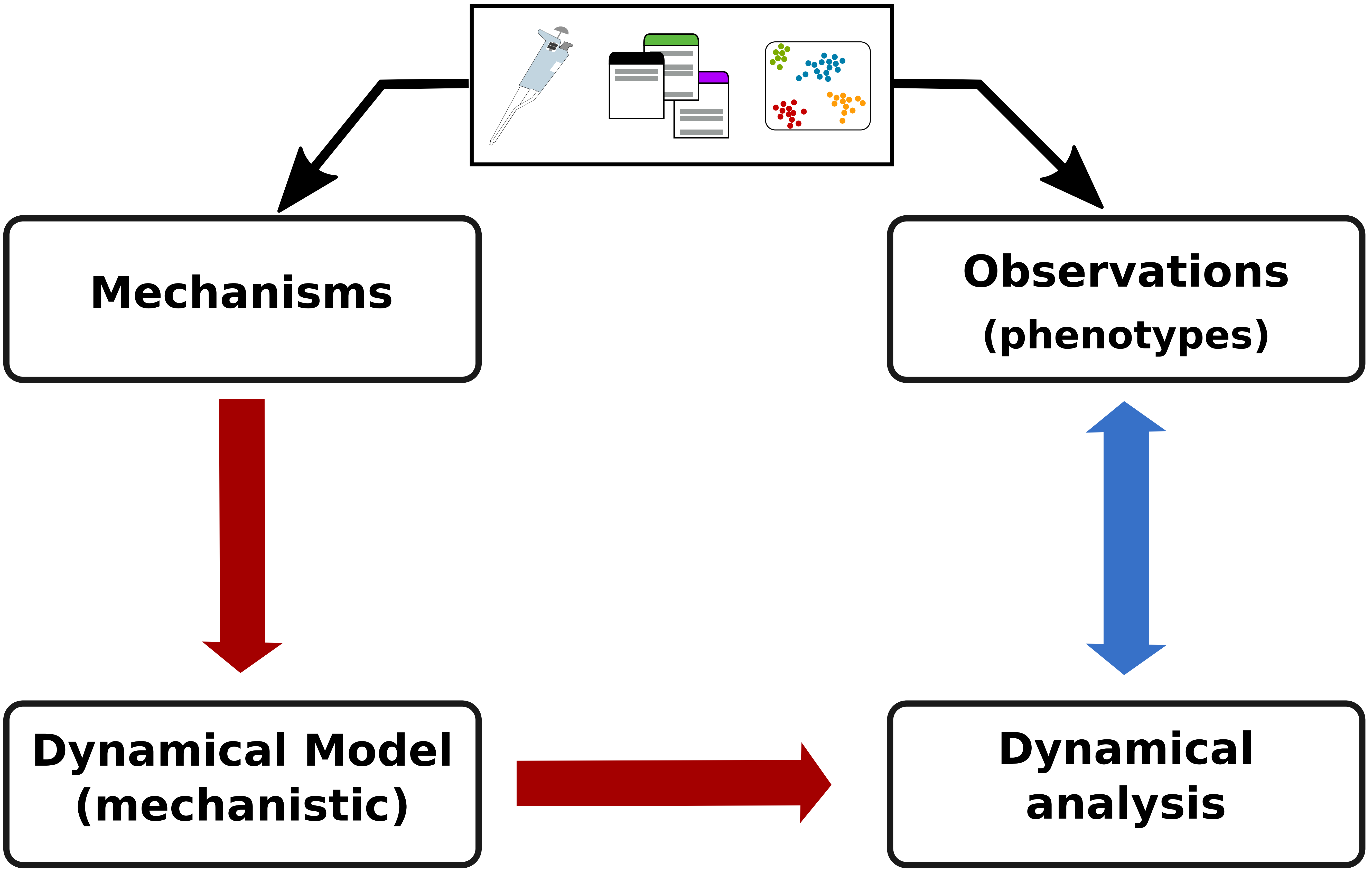
Qualitative Dynamical Models in Biology

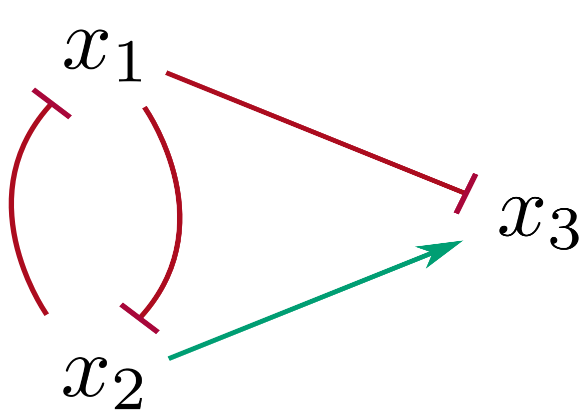


Logical modelling framework

Logical rules

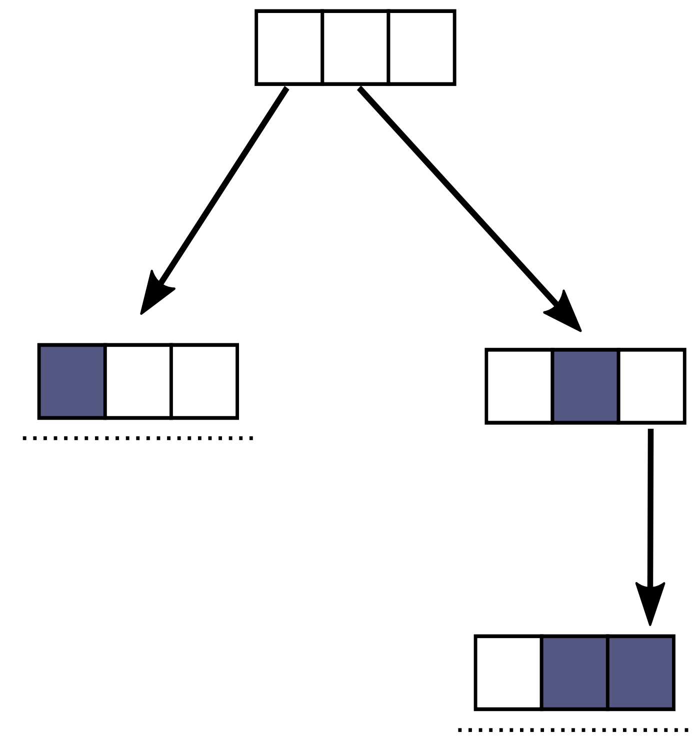
$$f_1(x) = \neg x_2$$
$$f_2(x) = \neg x_1$$
$$f_3(x) = \neg x1 \wedge x_2$$

Regulatory graph



Dynamics as State Transition Graph

$$x = (x_1, x_2, x_3)$$



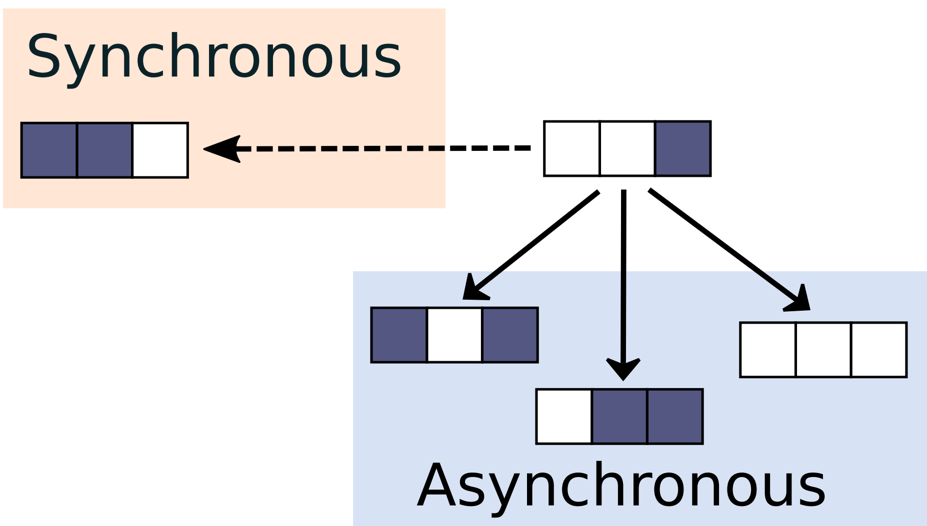
No quantitative parameters

Formal description of competing effects

Updating semantics

x: state	$\bar{x}^i$: flip i	$f(x) = \bar{x}^U$: image	$U = \{i : f_i(x) \neq x_i\}$

$x \to f(x)$



$\forall i \in U$: $x \to \bar{x}^i$

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Everything happens
at the same time

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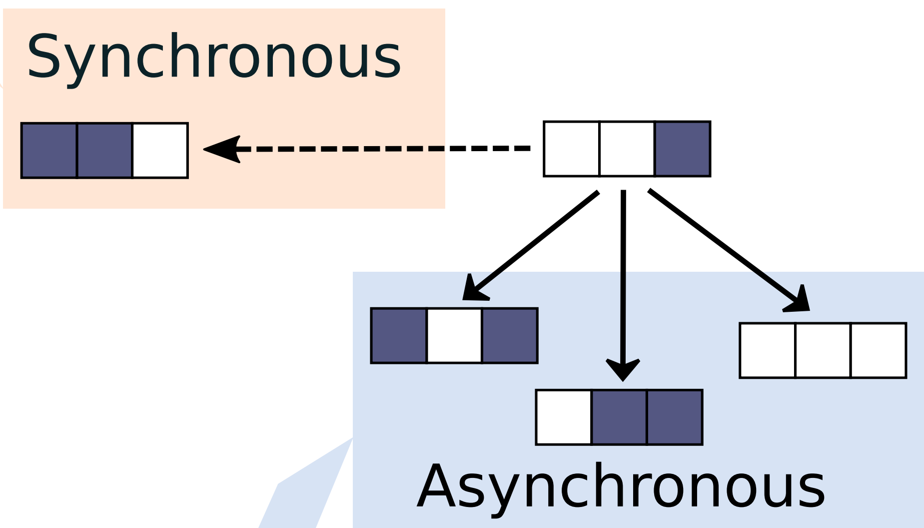

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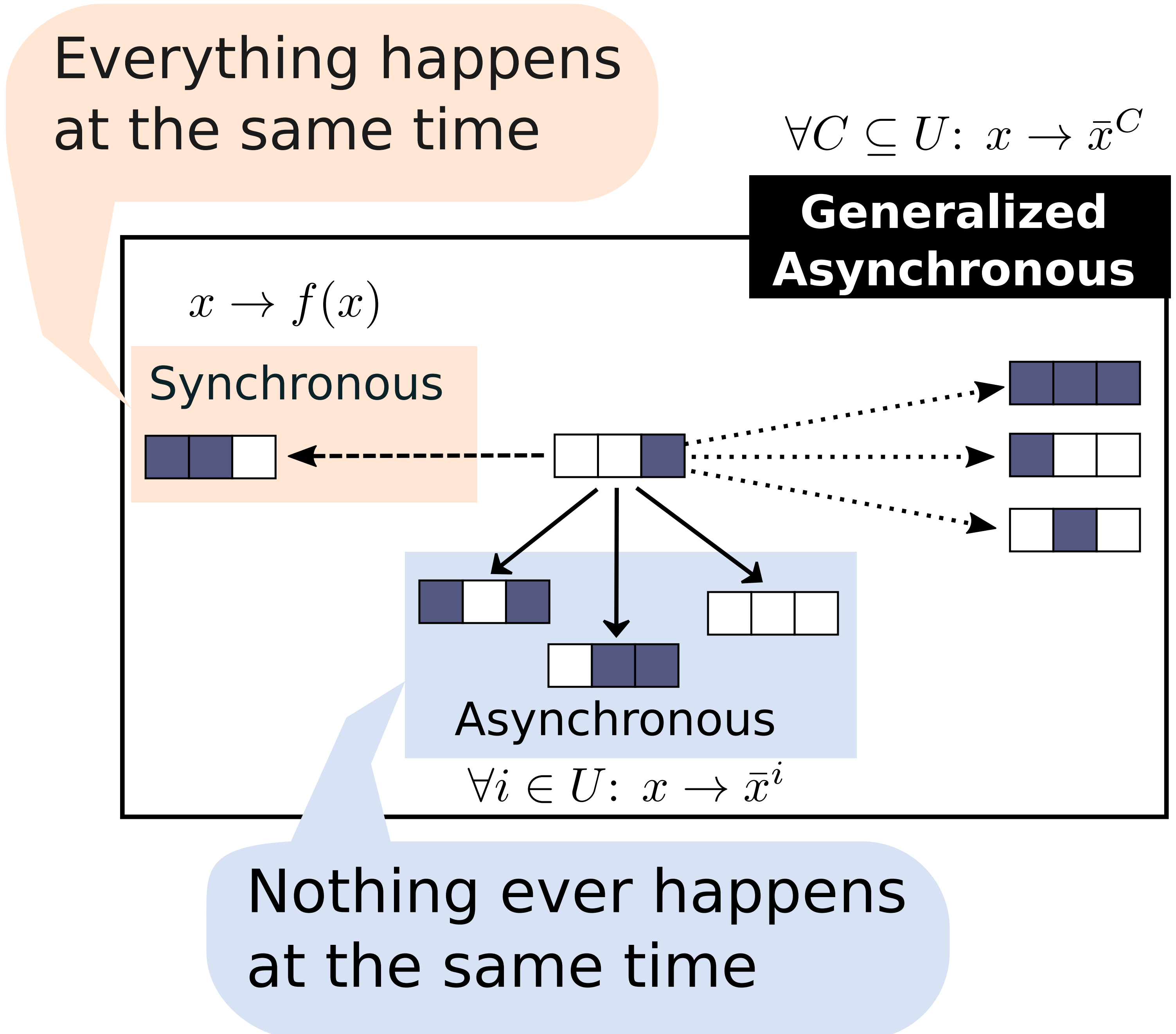

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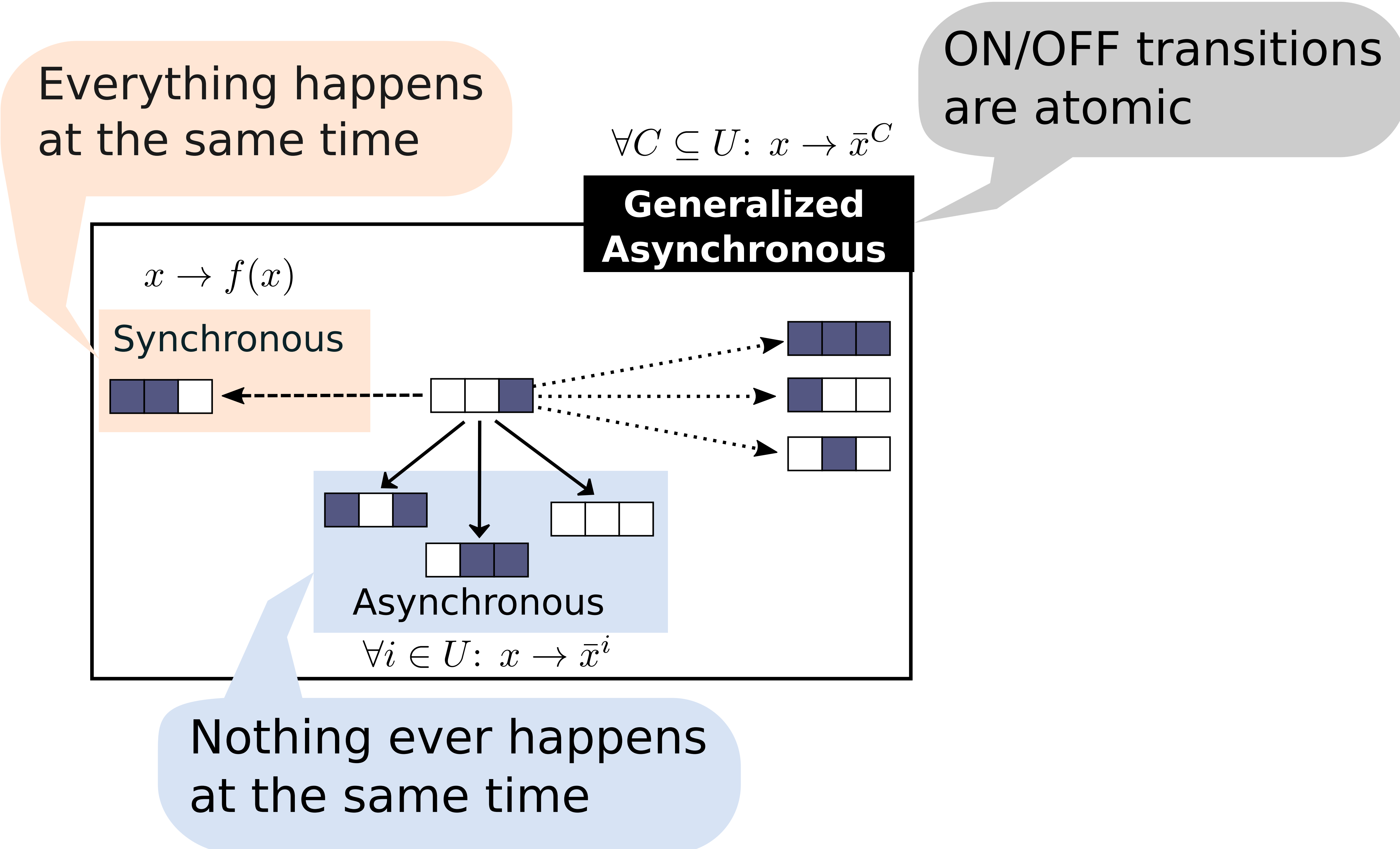

Updating semantics

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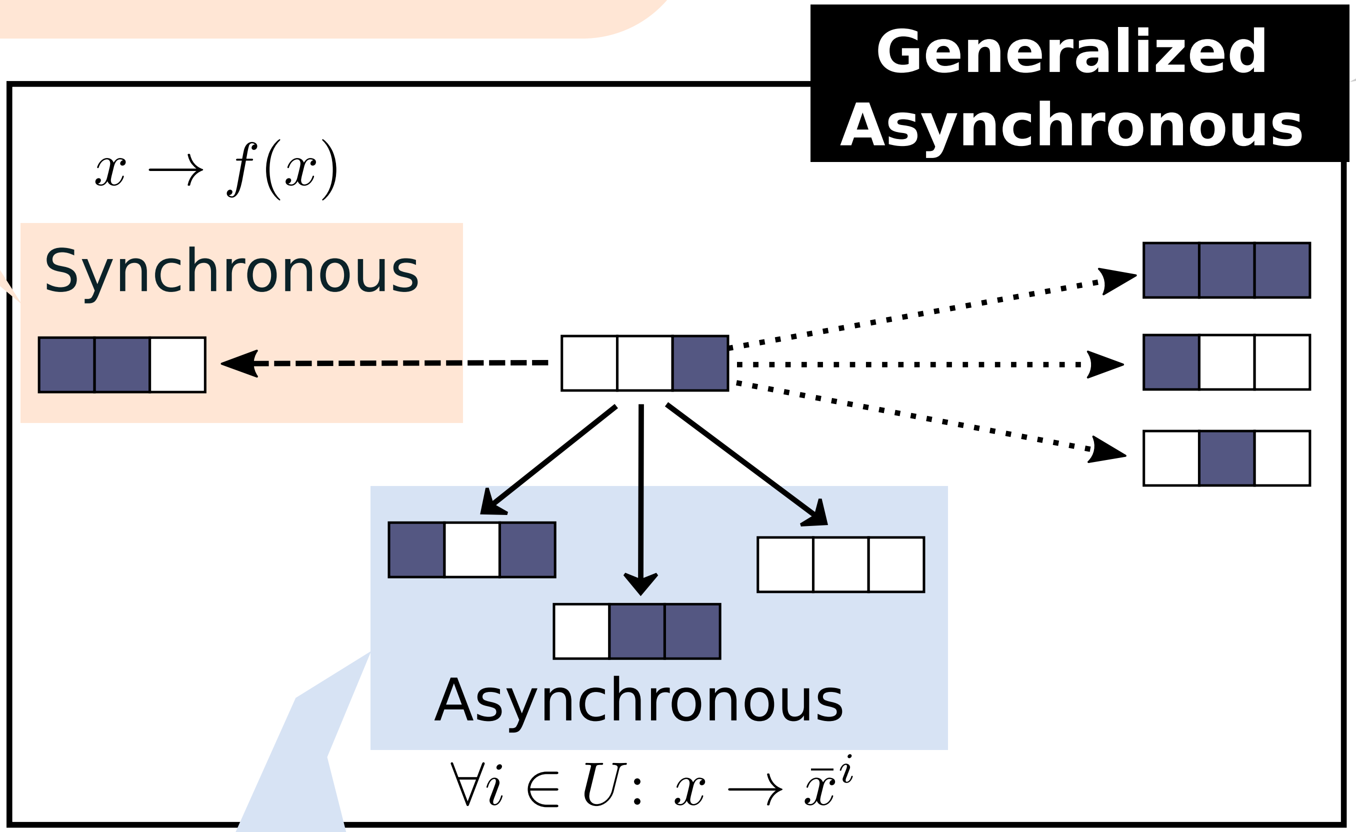
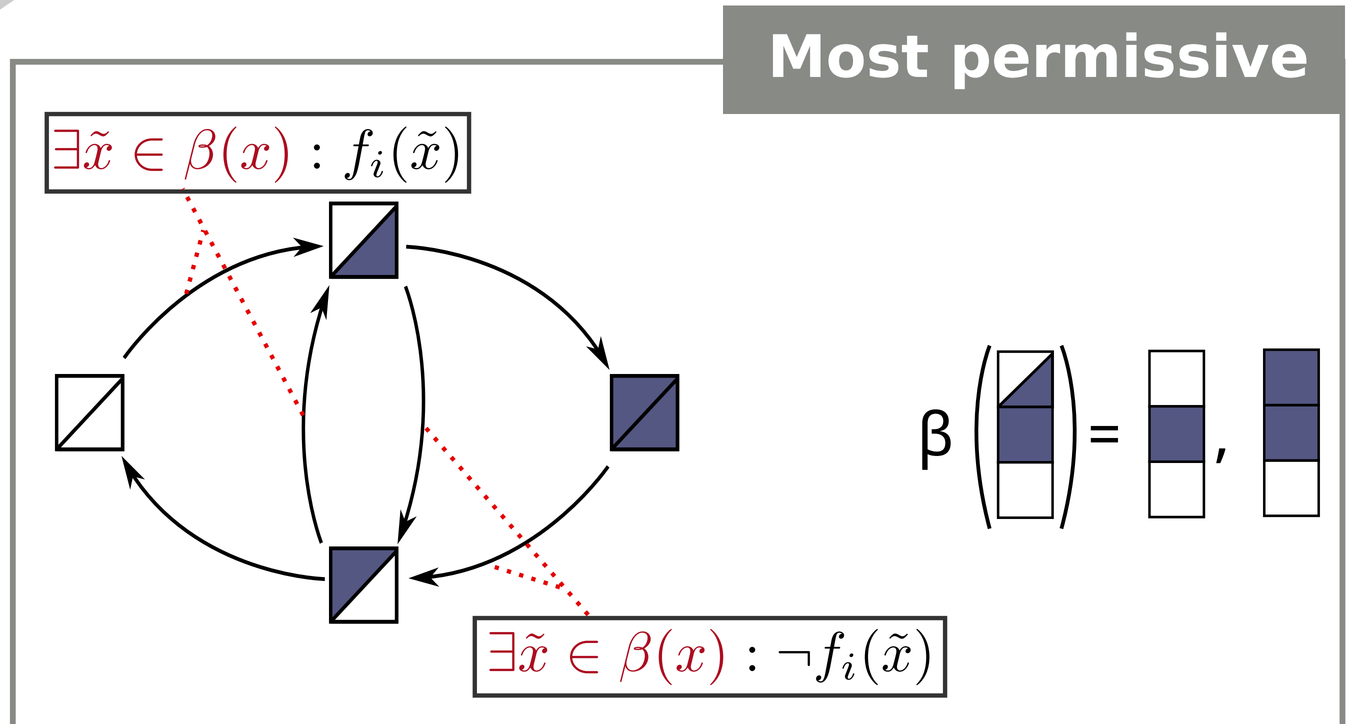
Everything happens at the same time

ON/OFF transitions are atomic

$\forall C \subseteq U$: $x \rightarrow \bar{x}^C$





Paulevé et al., Nat. Comm. (2020)

Nothing ever happens at the same time

Updating semantics

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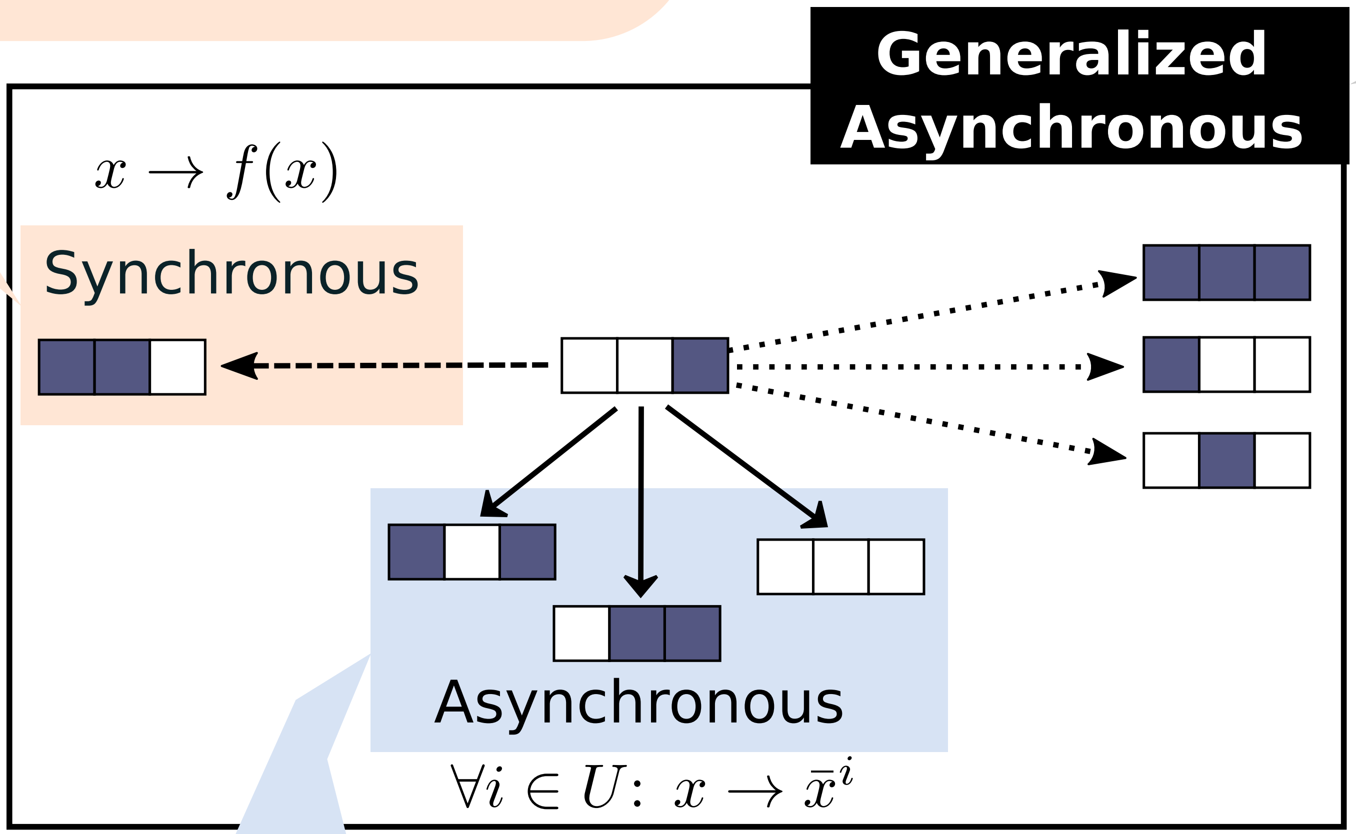
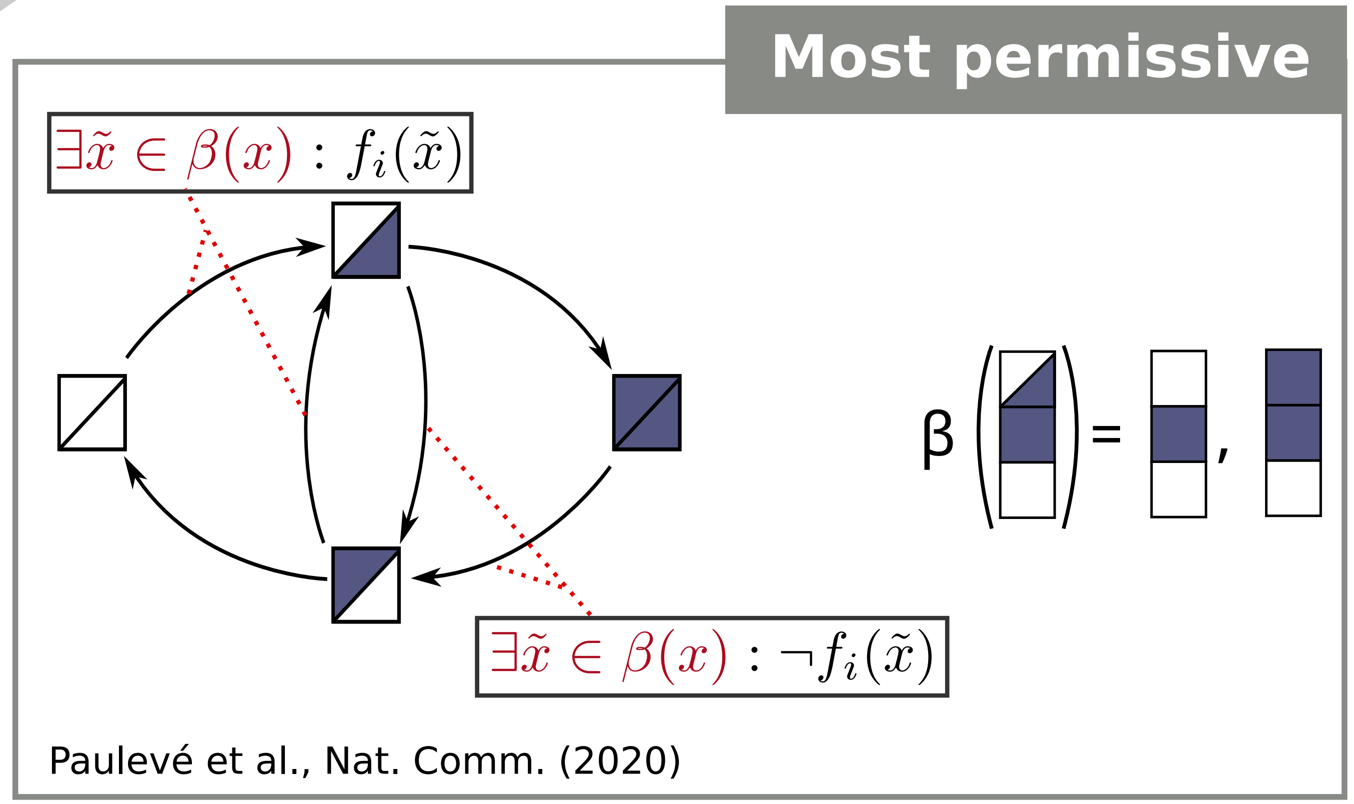




Nothing ever happens at the same time

Alternative trajectories

Kinetic assumptions

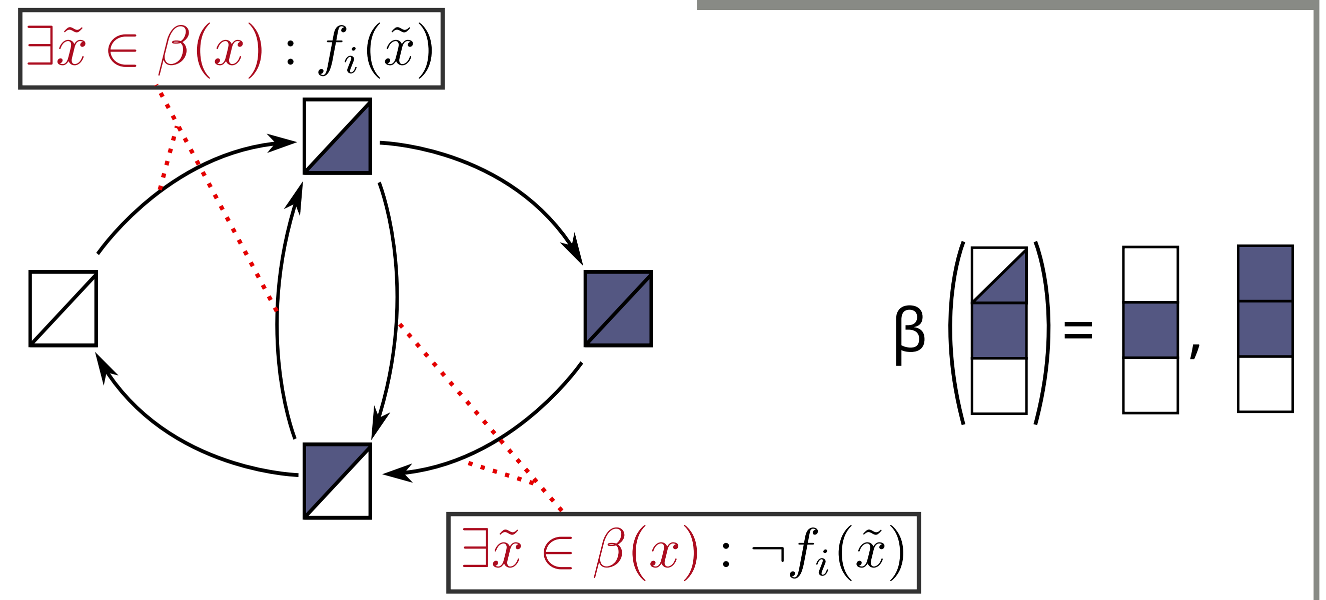
Updating semantics

Huge number of trajectories

Low computational complexity
- attractors
- reachability

Multivalued refinements

Most permissive



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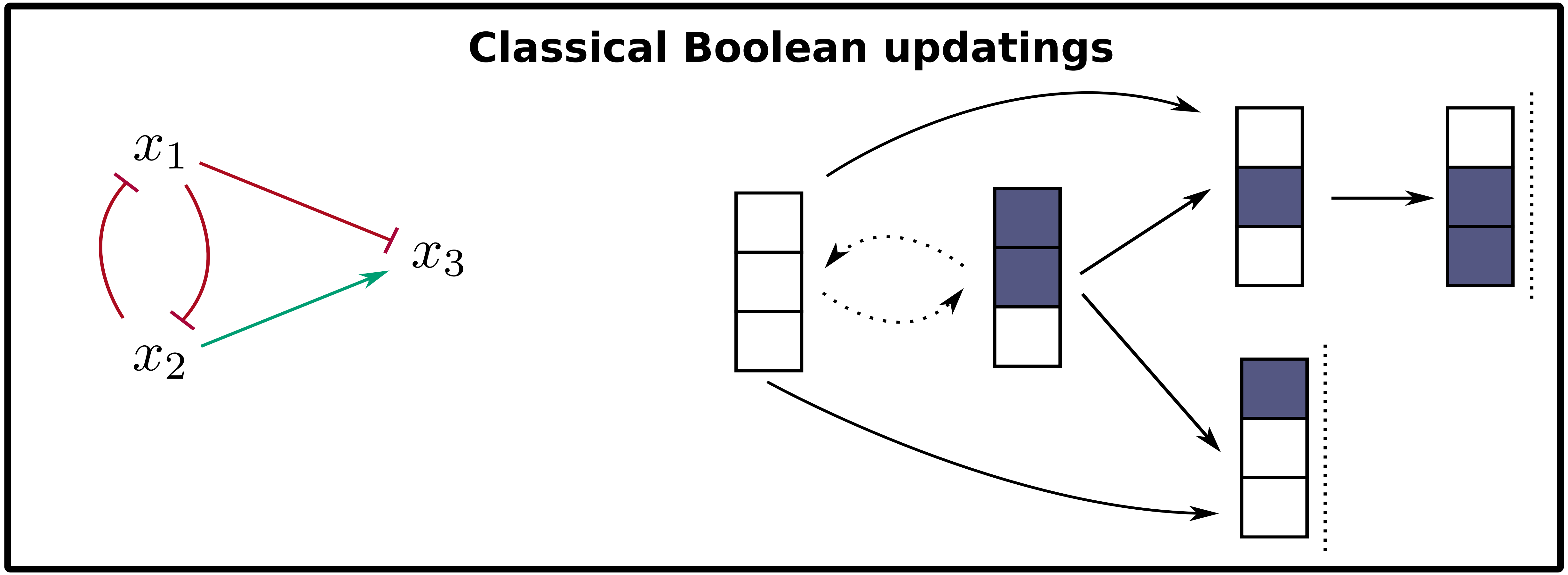
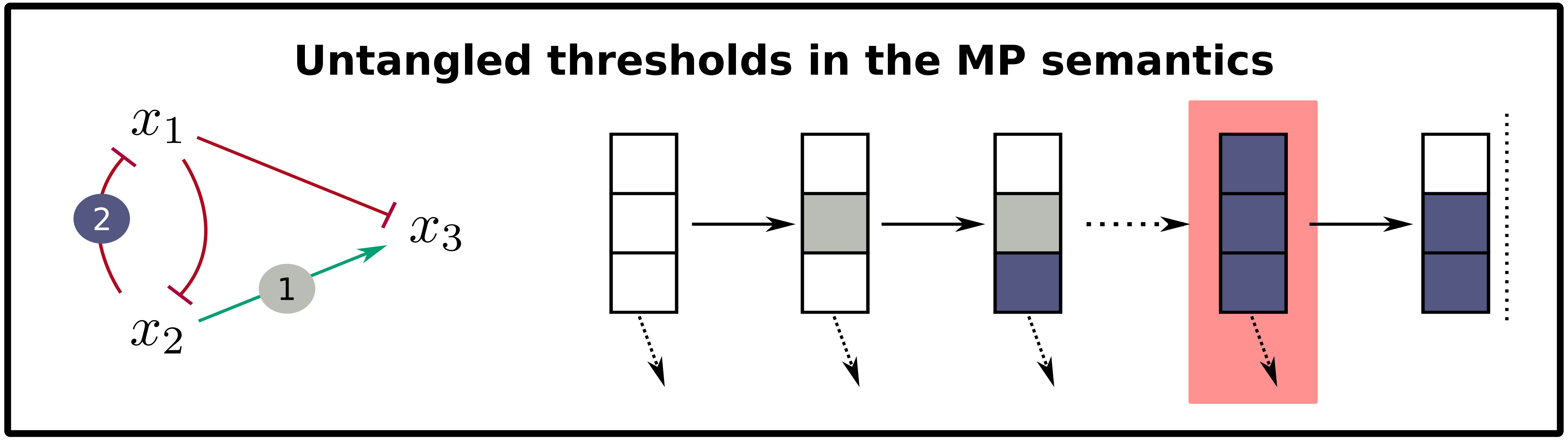
Alternative trajectories

Kinetic assumptions

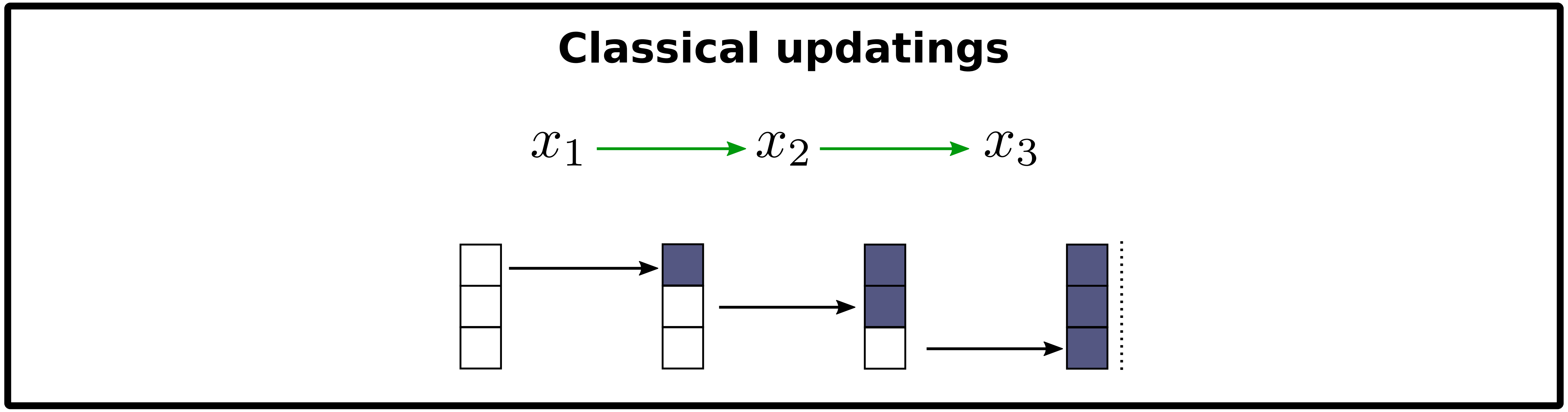
Trajectories with untangled thresholds

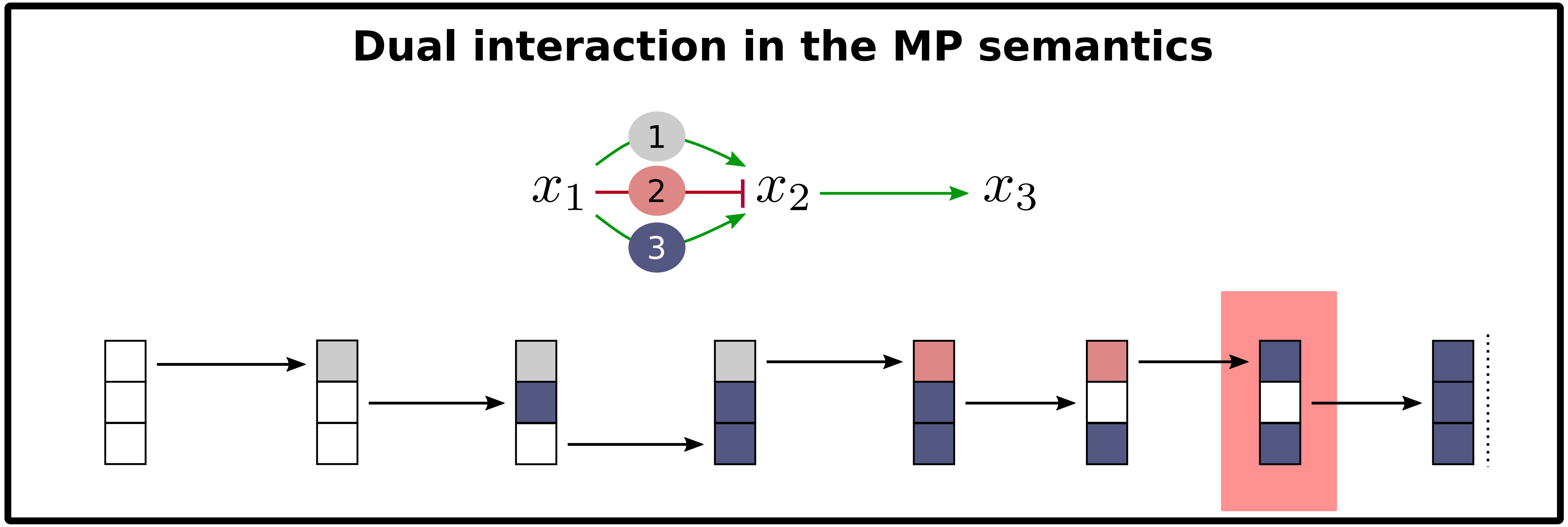




Refinements reveal effect of separate thresholds

Trajectories with dual interactions



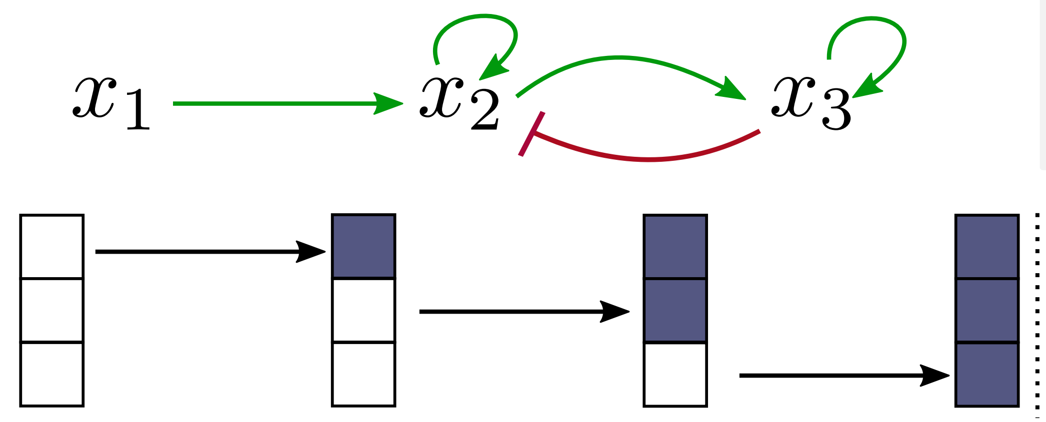


Refinements can introduce dual interactions

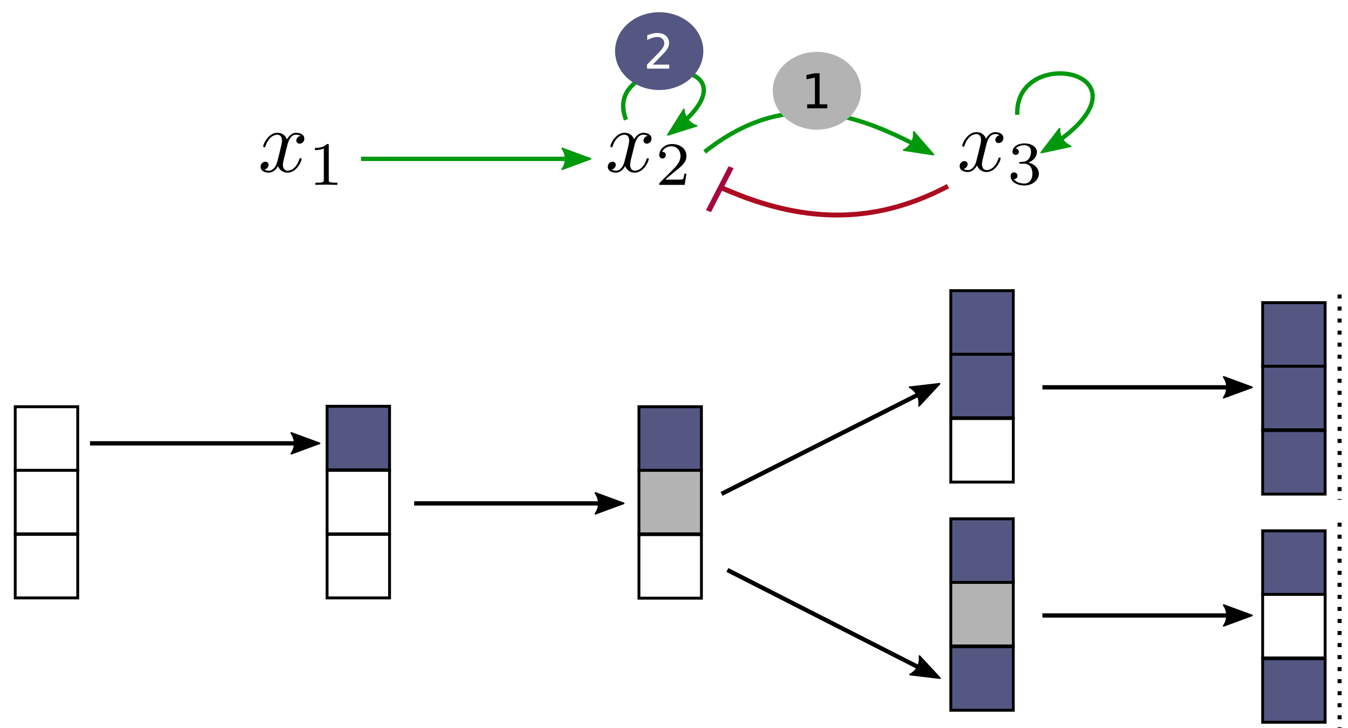
Stable states/patterns seem special

Classical updatings

$$f_1 = 1$$
$$f_2 = x_1 \wedge (x_2 \vee \neg x_3)$$
$$f_3 = x_2 \wedge x_3$$

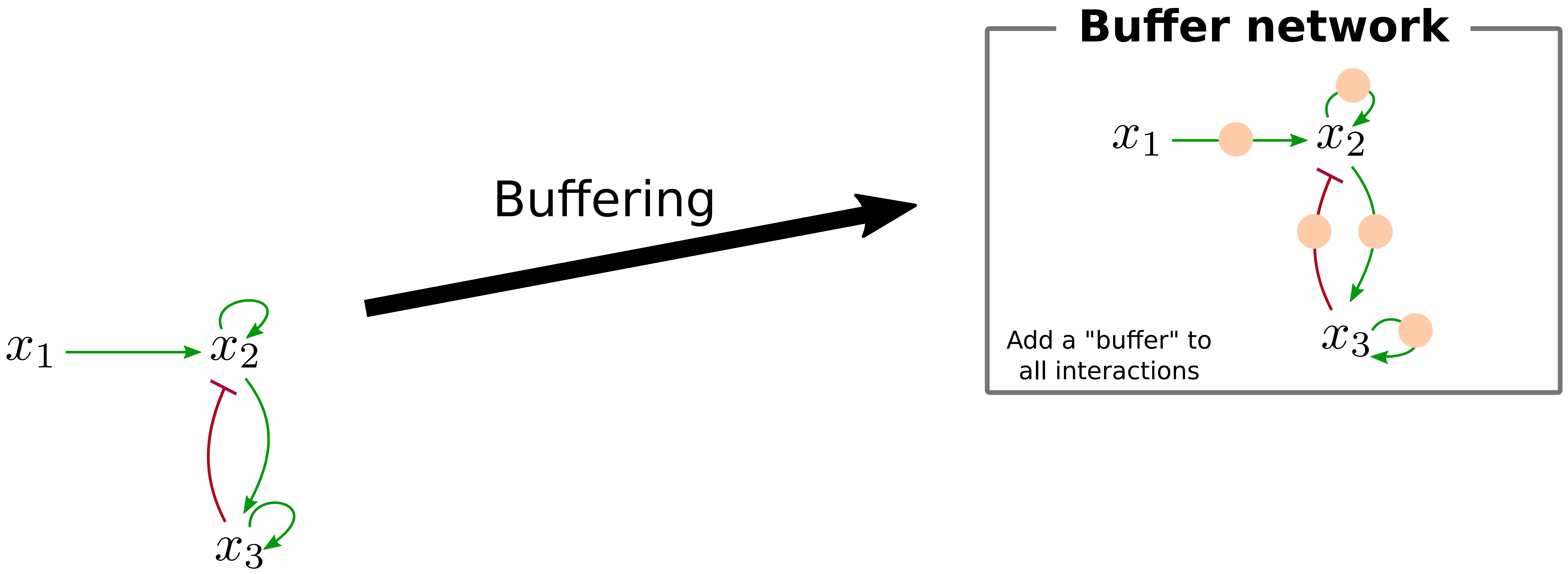


Reachable without dual interaction



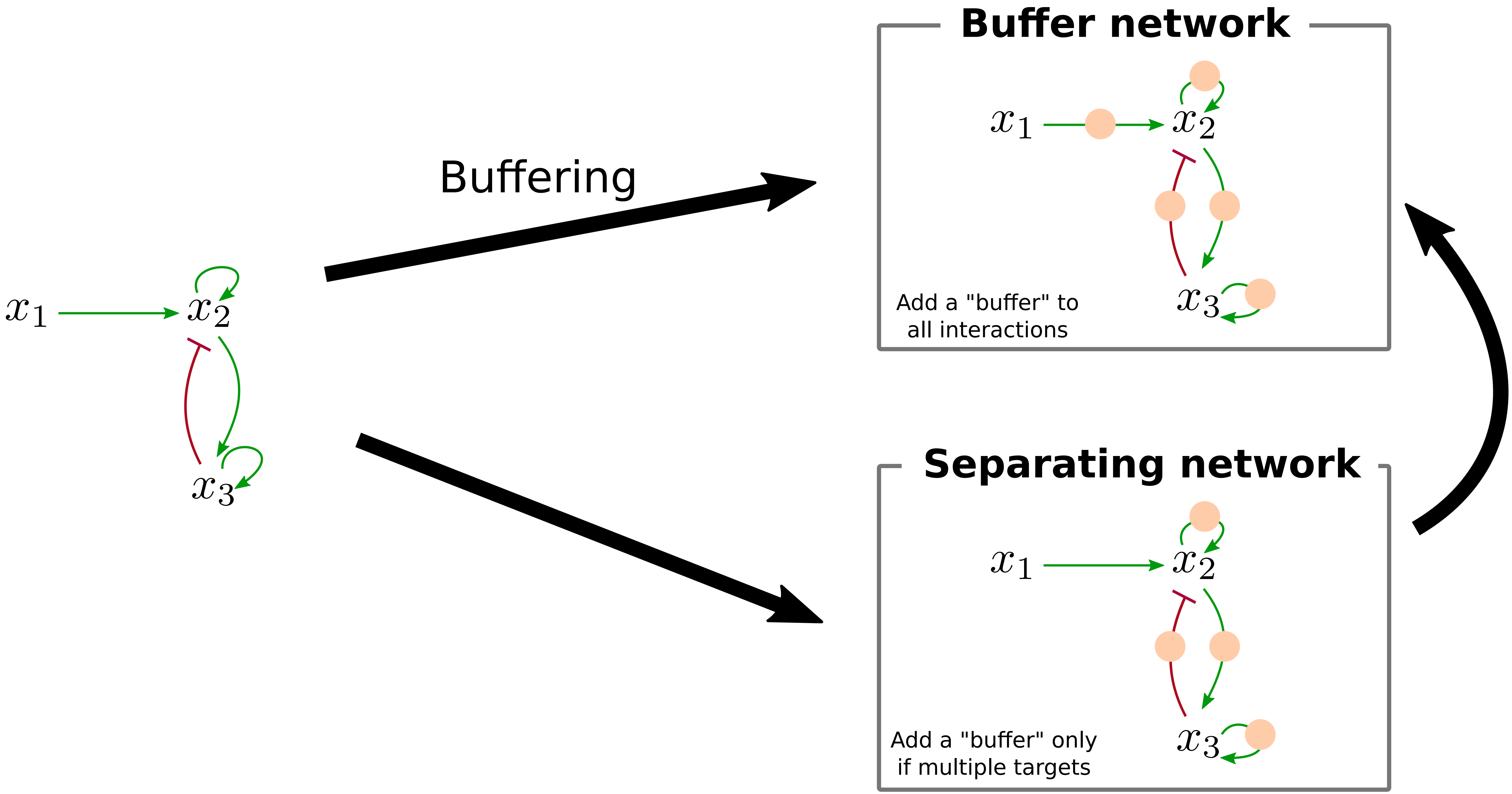
Are stable patterns always easier to reach?

Buffer networks



Asynchronous updating of the extended model

Buffer networks



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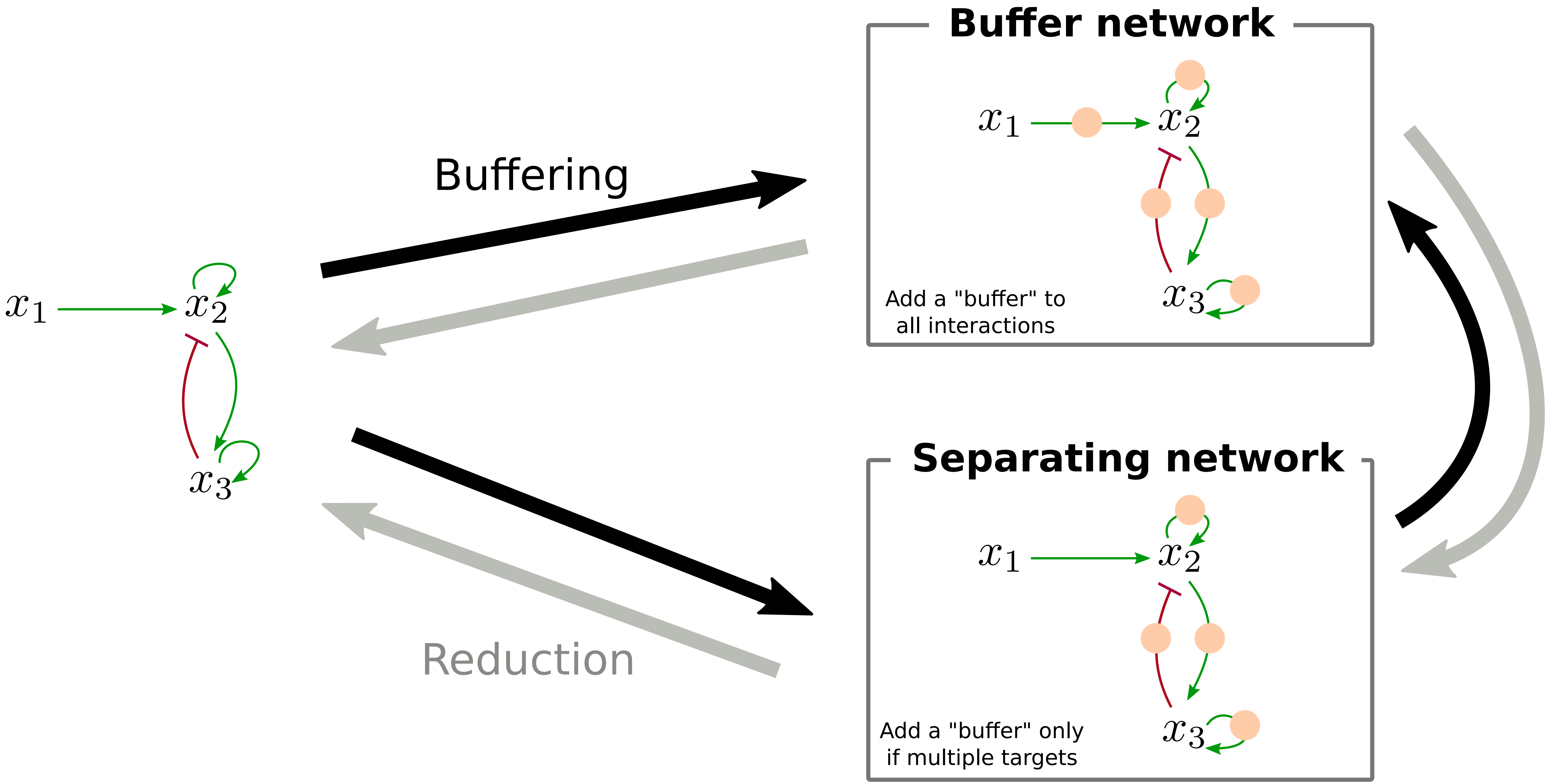
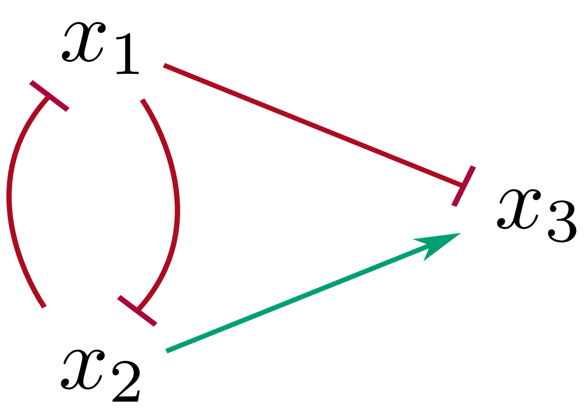


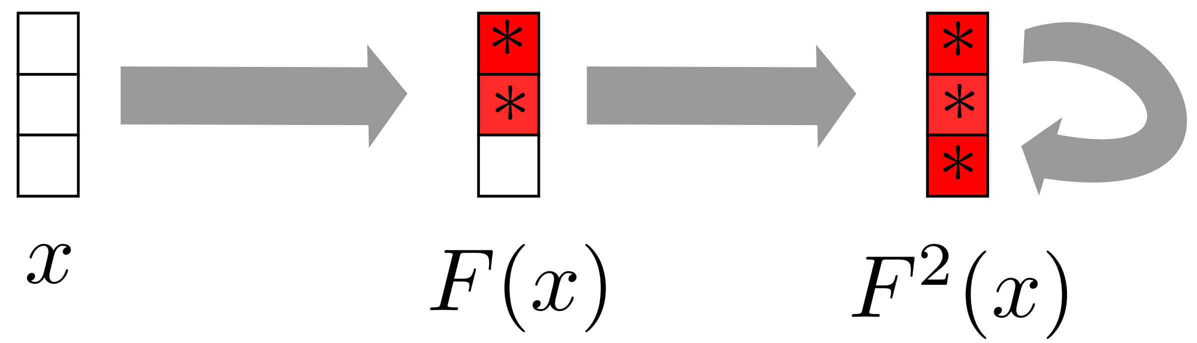
Asynchronous updating of the extended model

Enclosing stable pattern



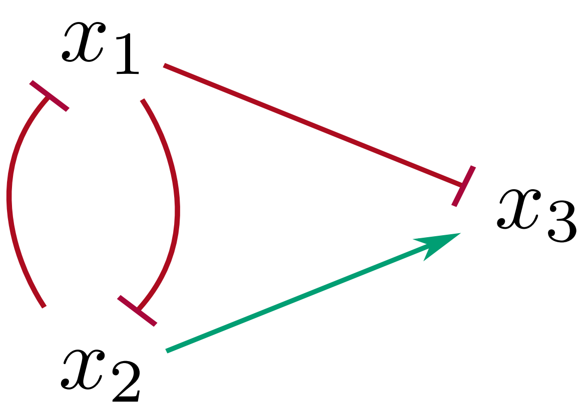
Extend f to patterns

$$F_i(p) = \begin{cases} * & \text{if } p_i = *, \\ * & \text{if } \exists x \in p : f_i(x) \neq p_i, \\ p_i & \text{otherwise.} \end{cases}$$



$F^n(x)$ is the smallest stable pattern containing the state x

Enclosing stable pattern



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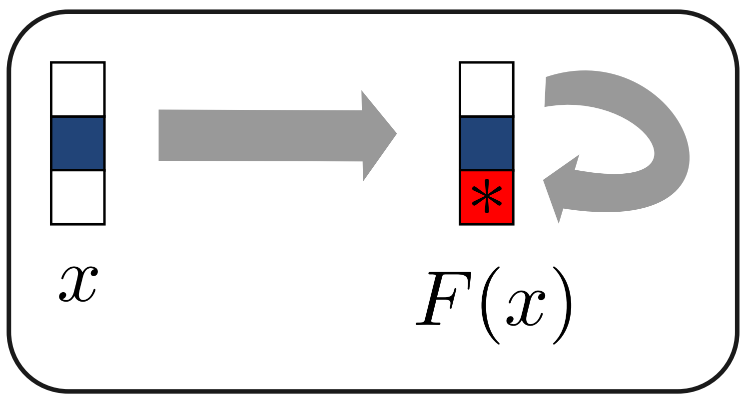

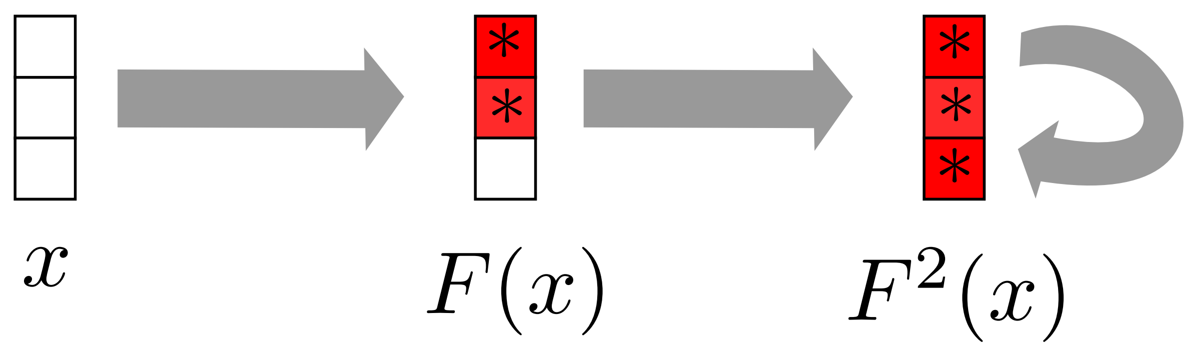

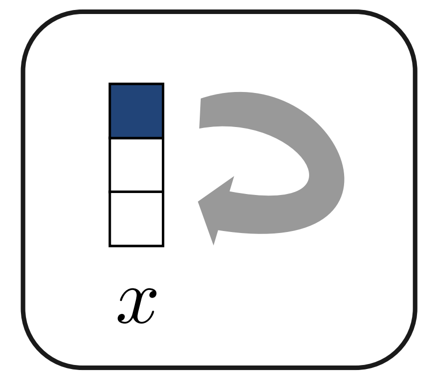

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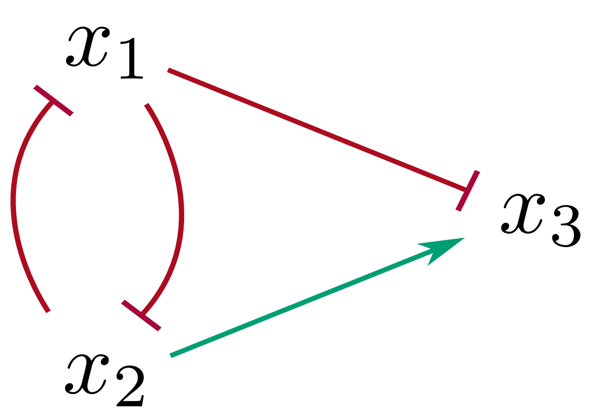
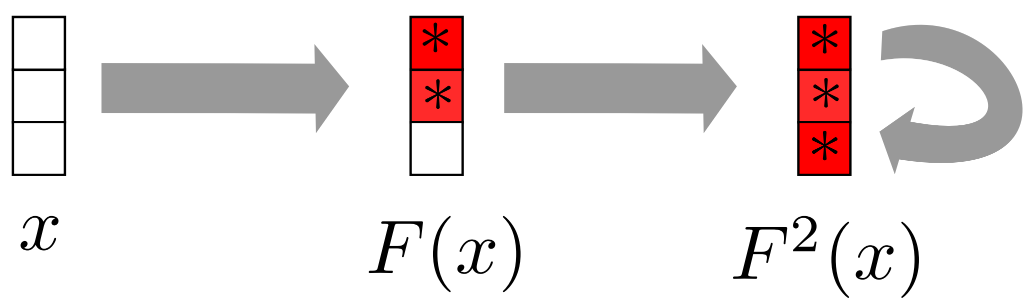
Partial order on transitions



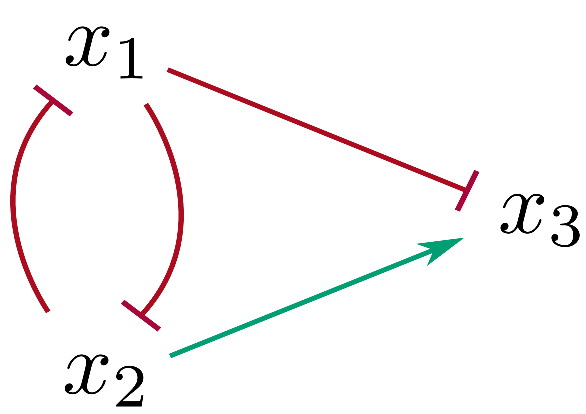


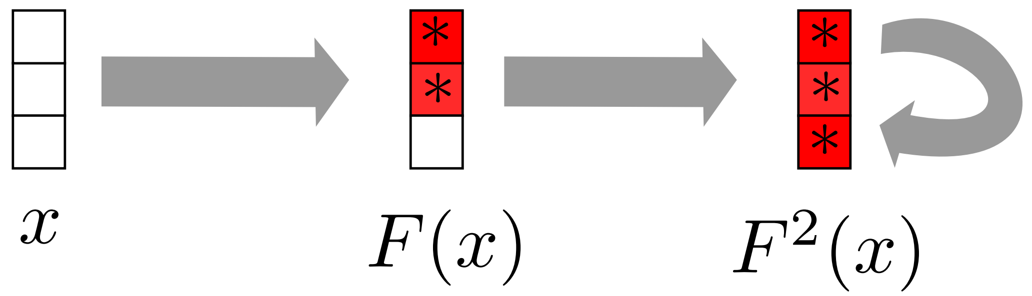
x_1

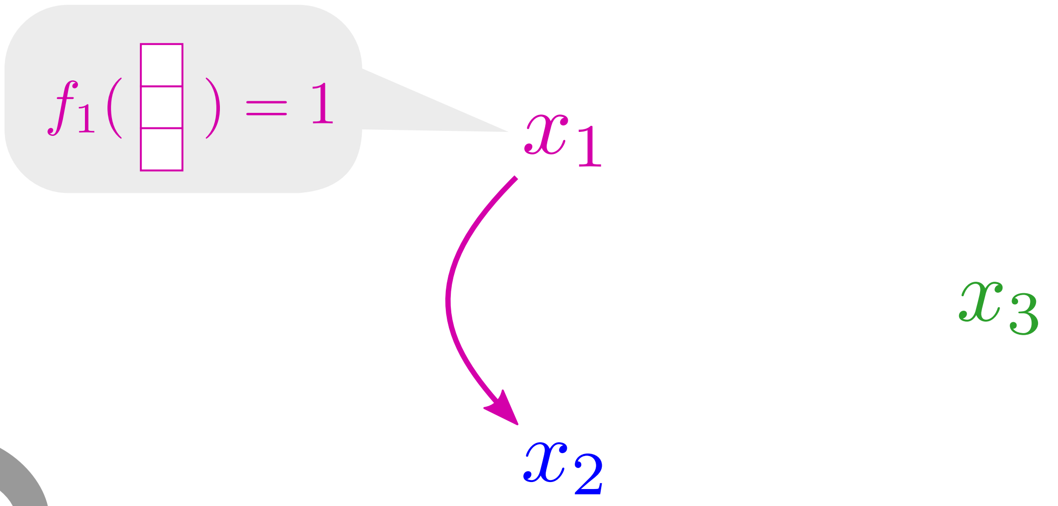
x_3

x_2

Partial order on transitions







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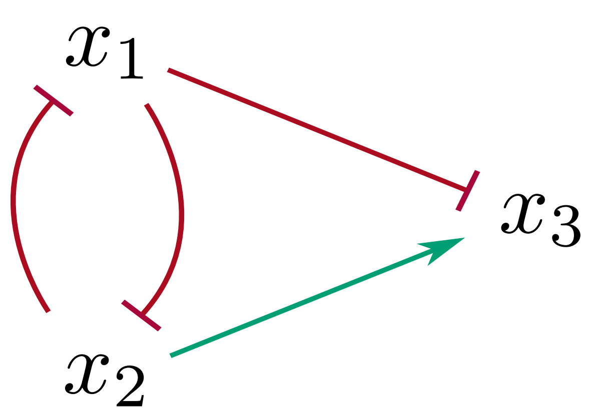

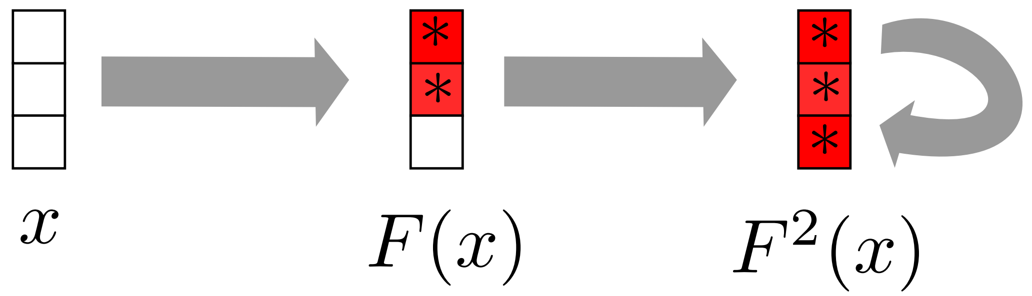

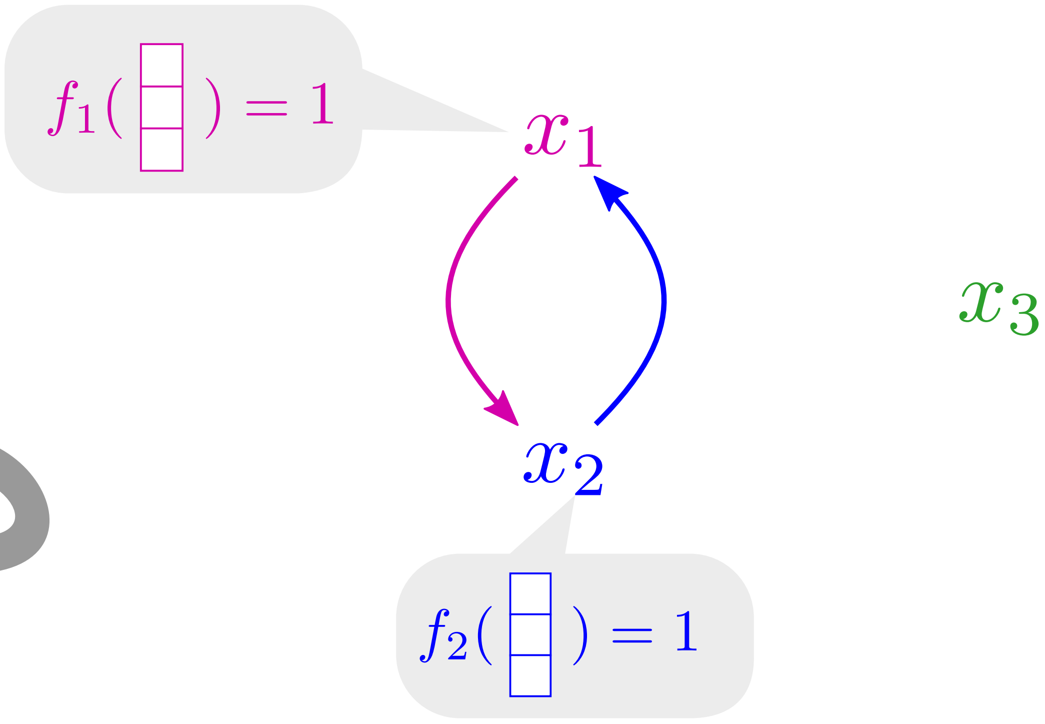

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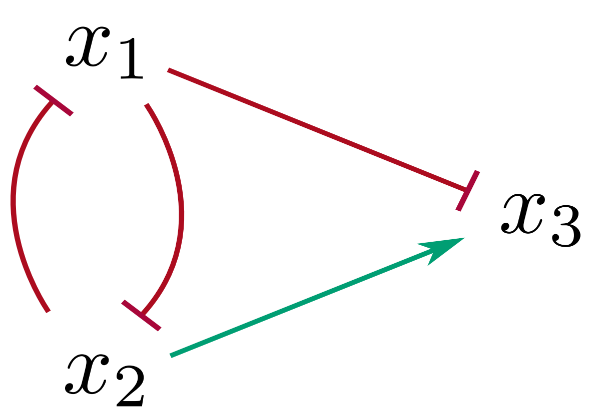

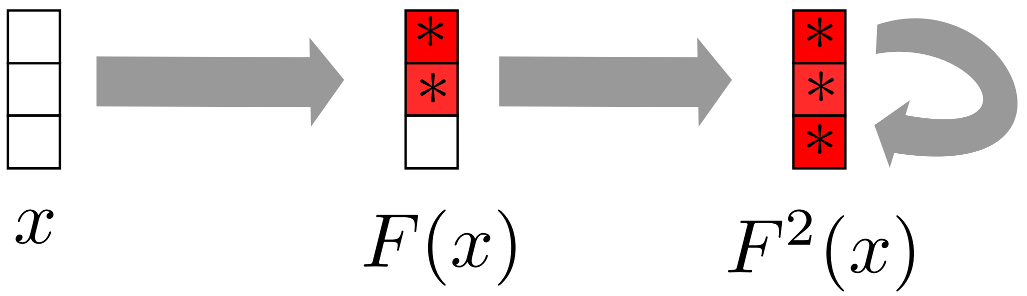

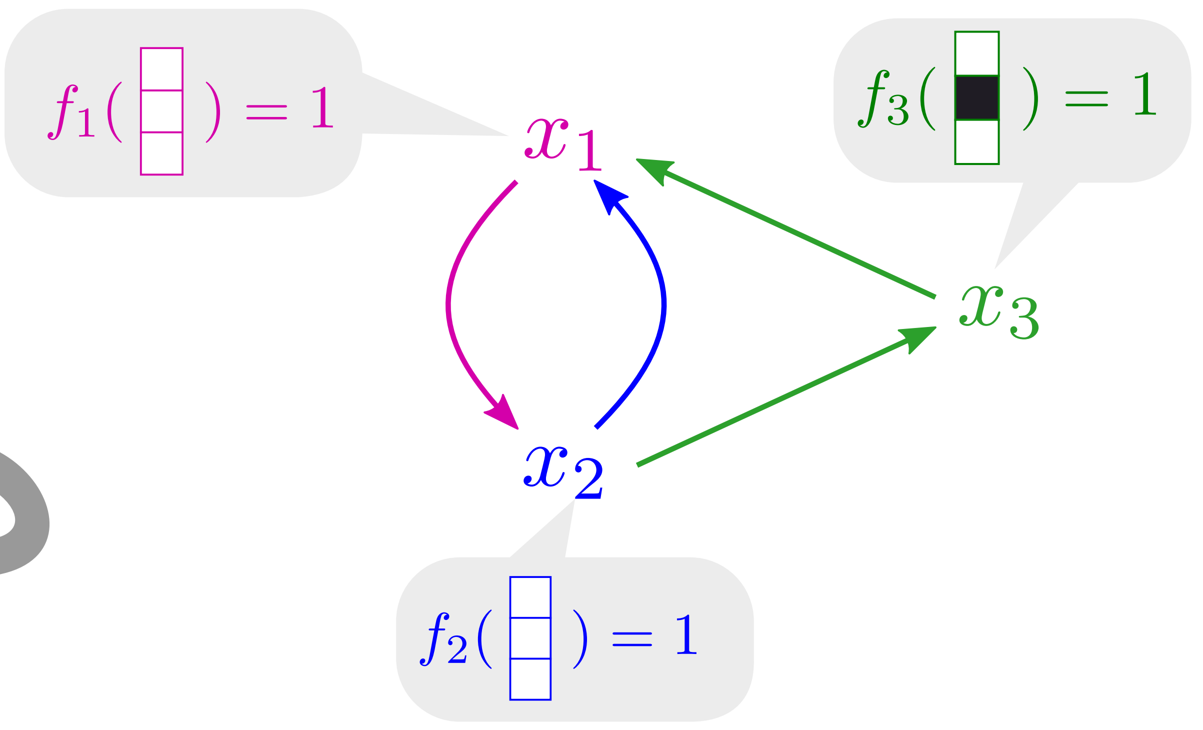

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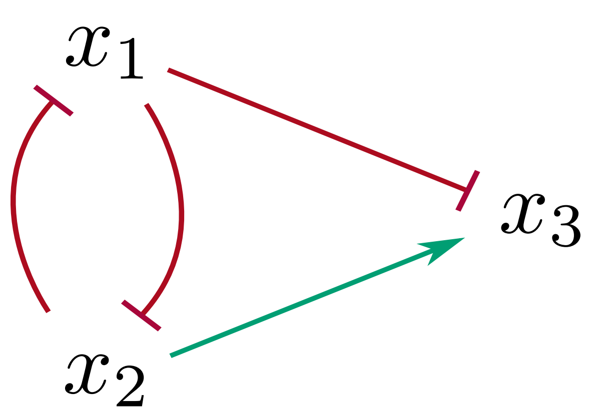
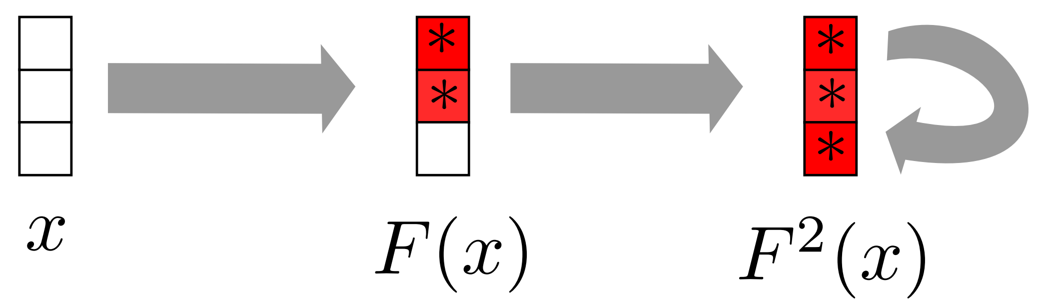
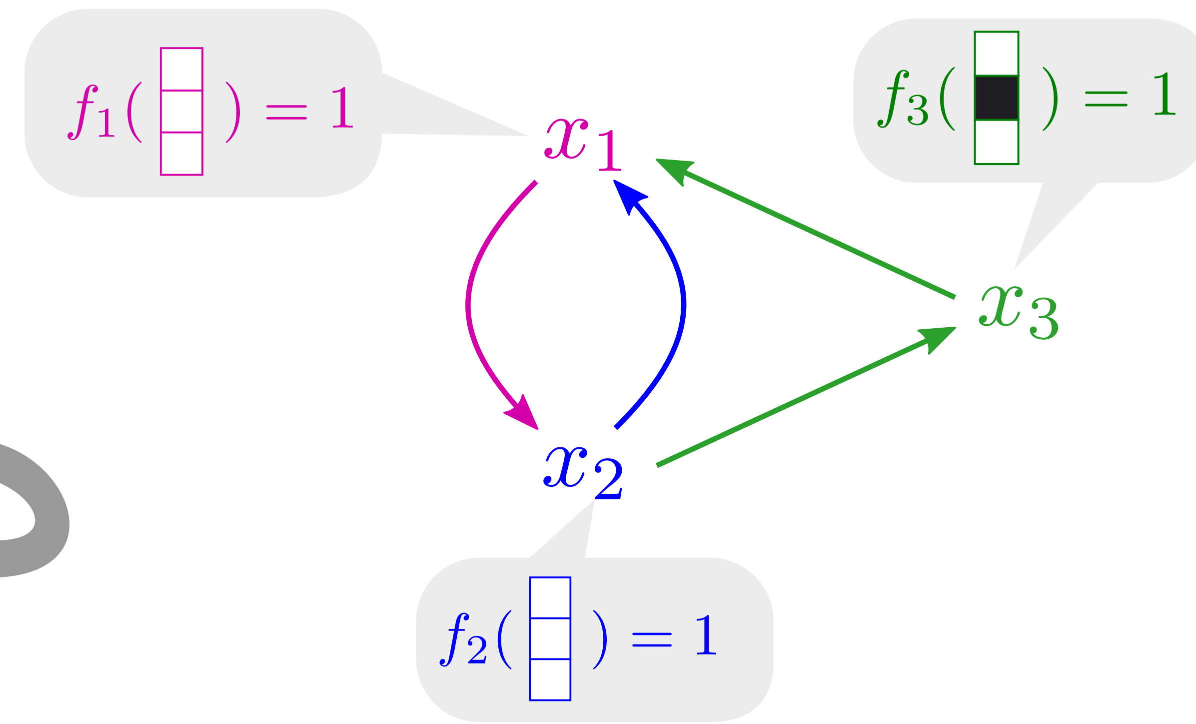
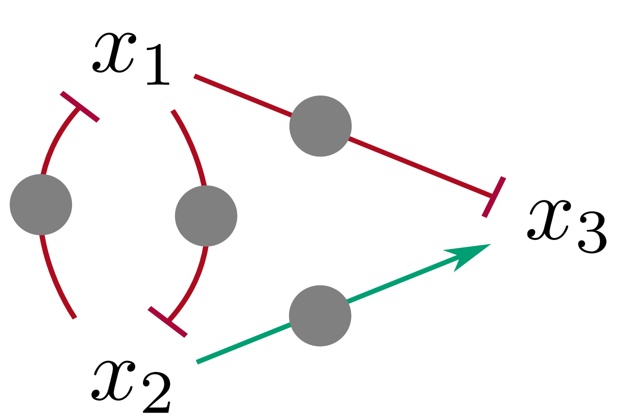
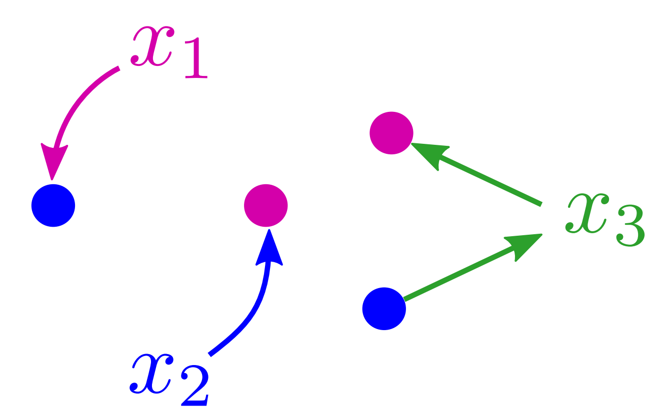








Same constraints
on regulators



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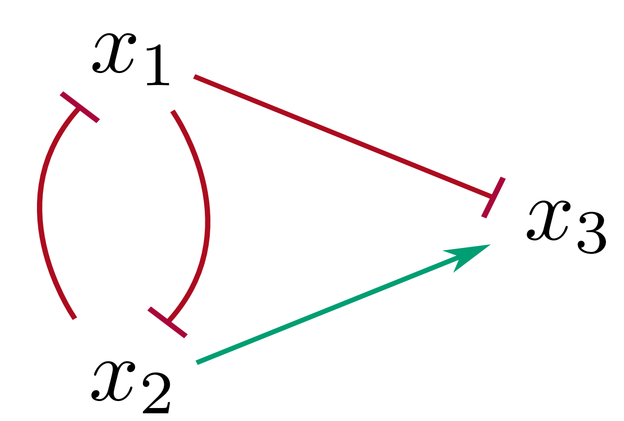
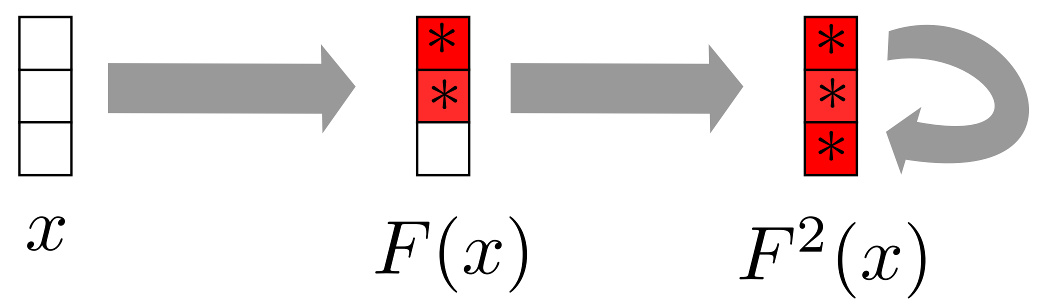
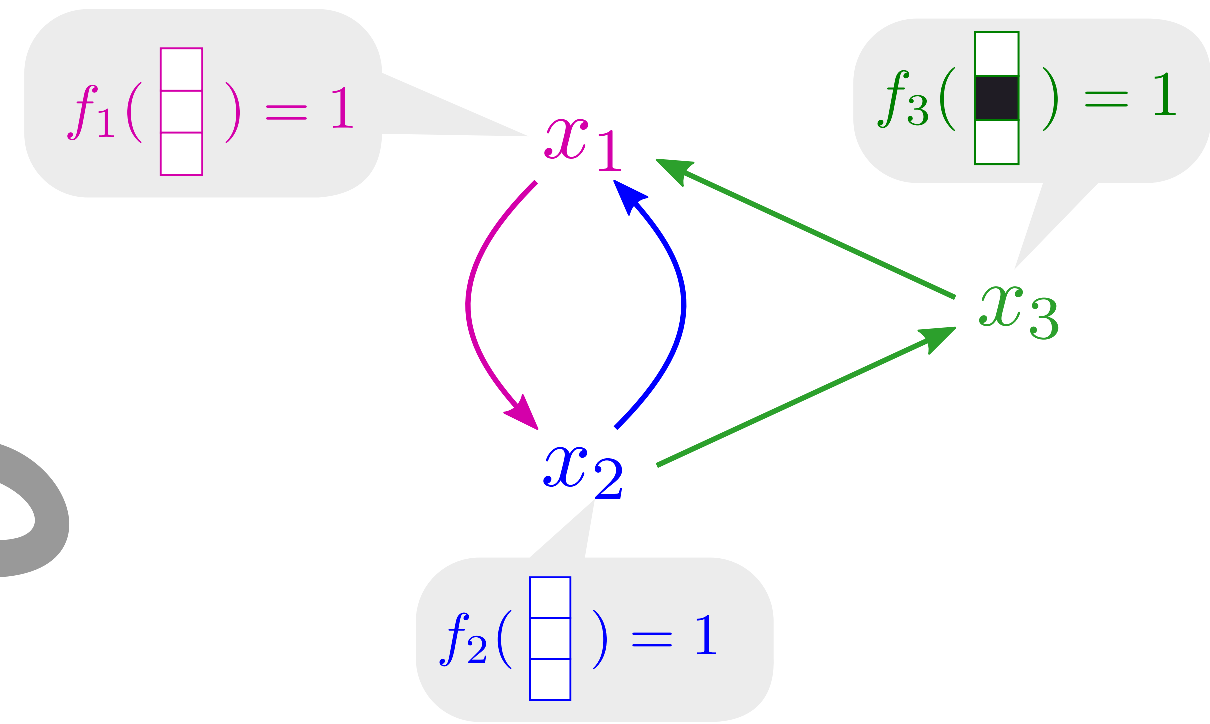
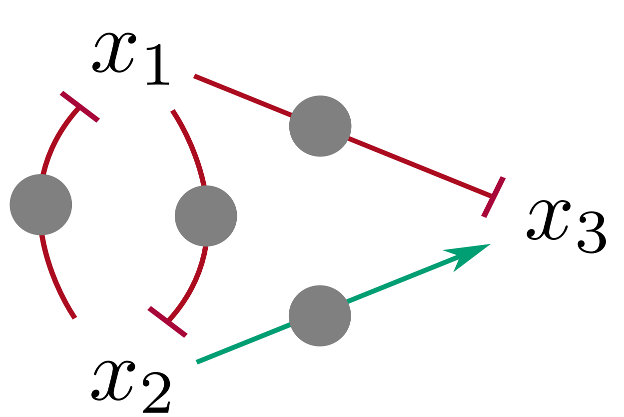


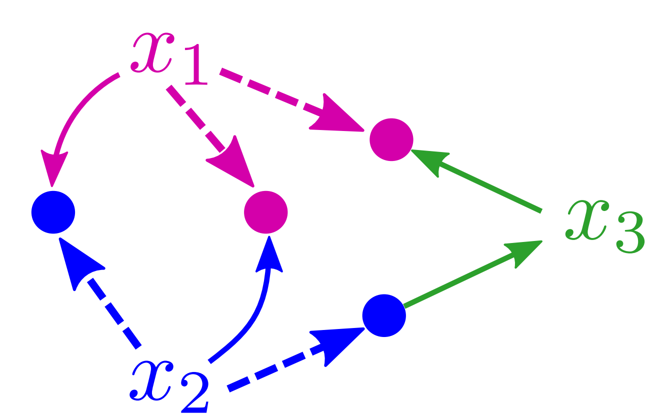






Same constraints on regulators

Buffers always follow
(for a consistent initial state)



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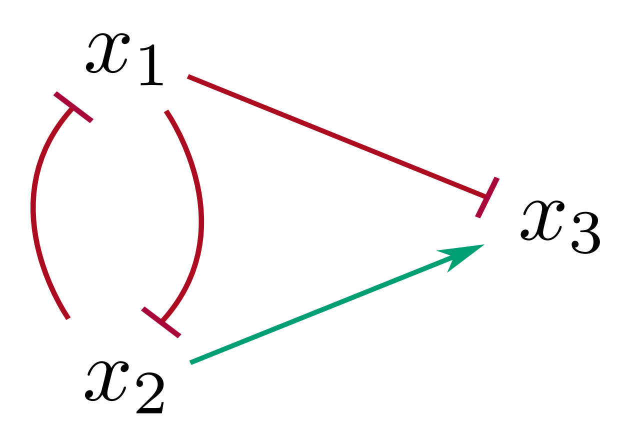

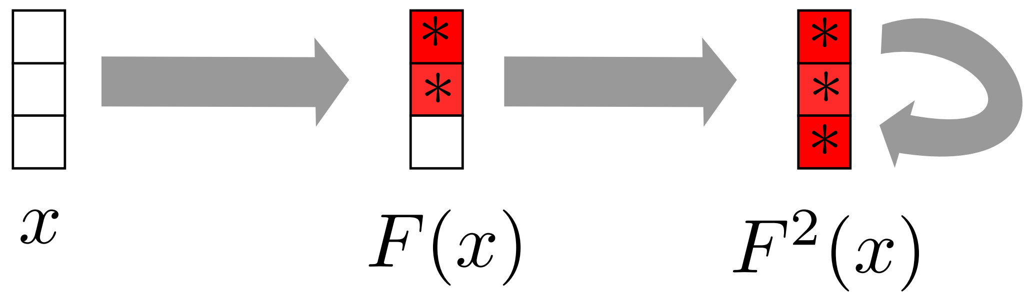

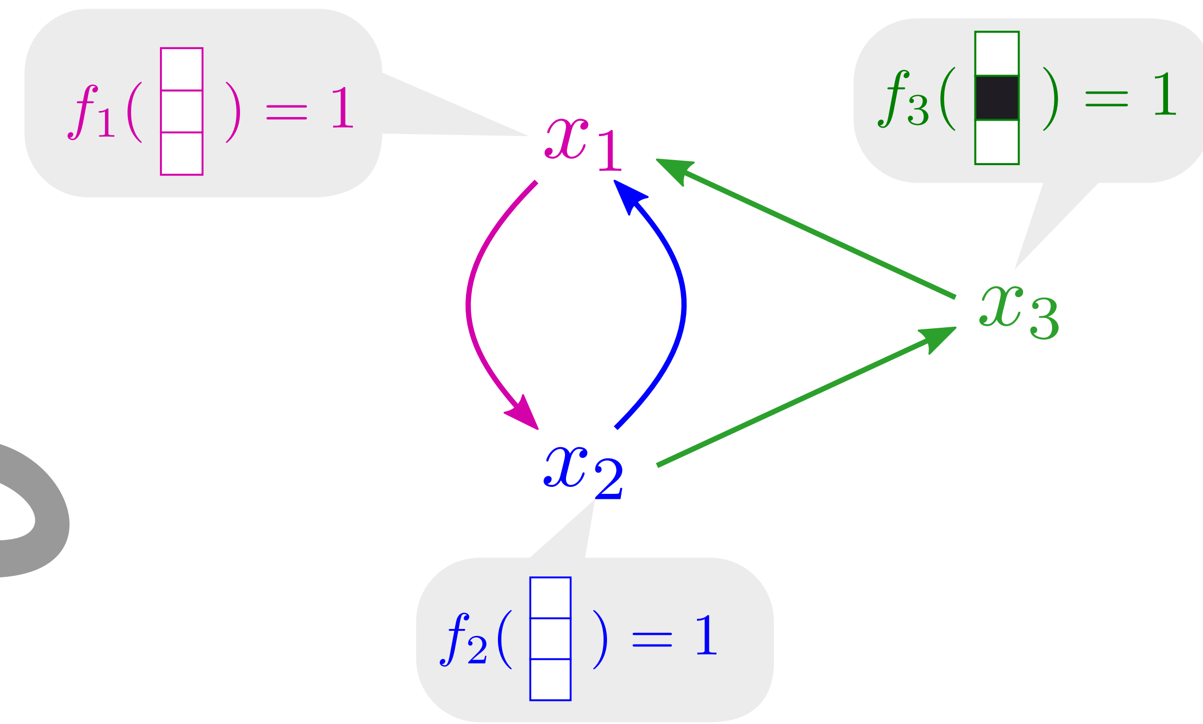

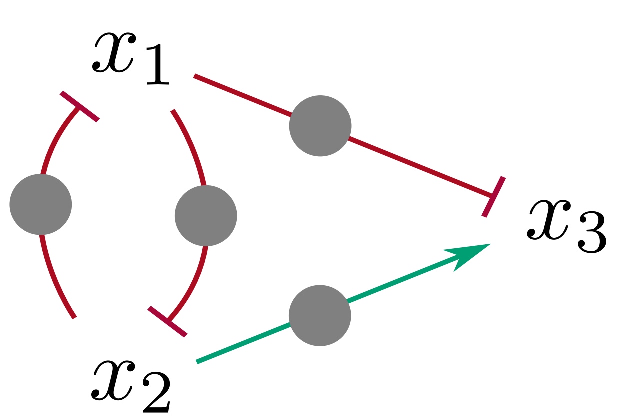

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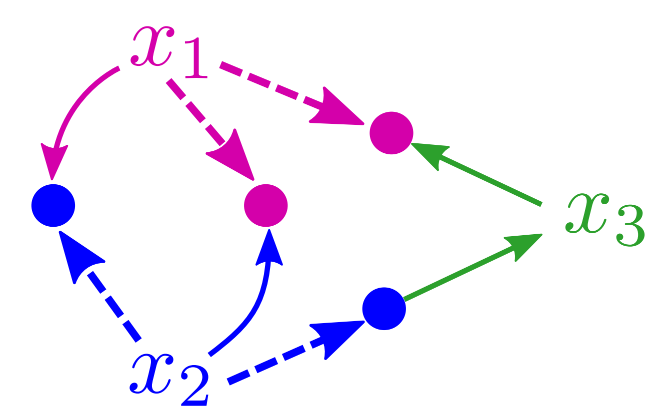
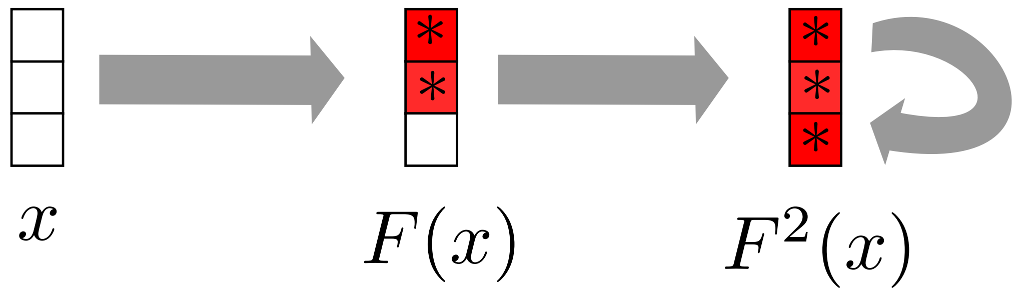
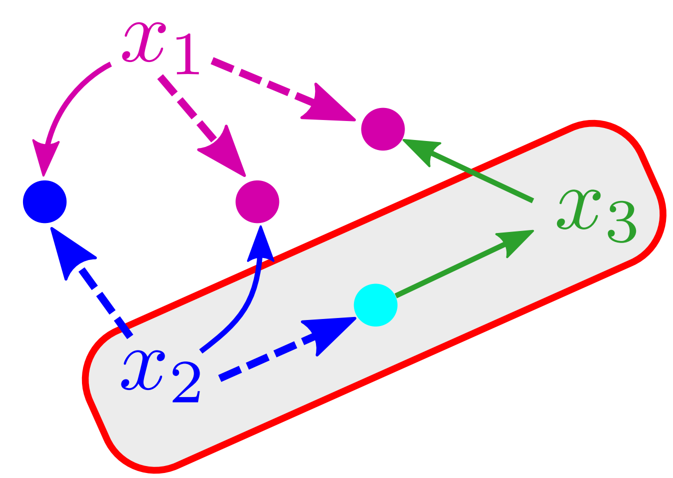


Buffers eliminate cycles in the partial order graph

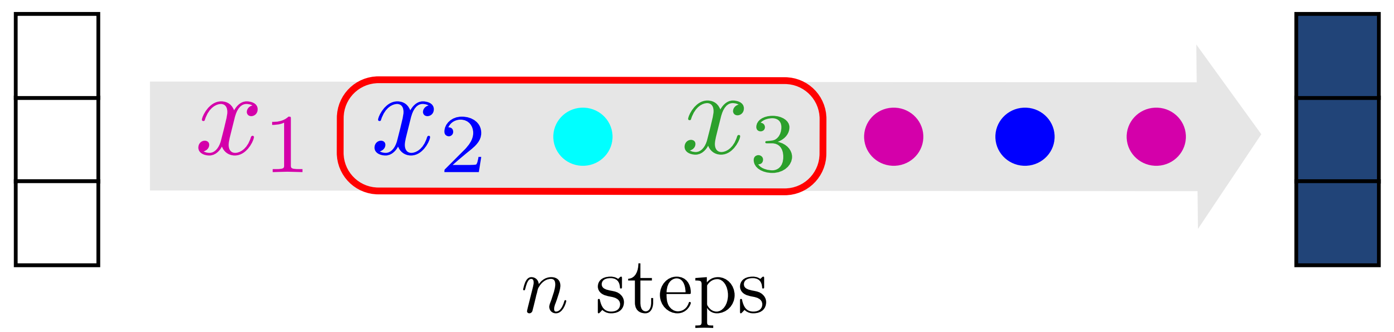
Reaching the opposing corner



Acyclic partial order



Trajectory to the opposing corner



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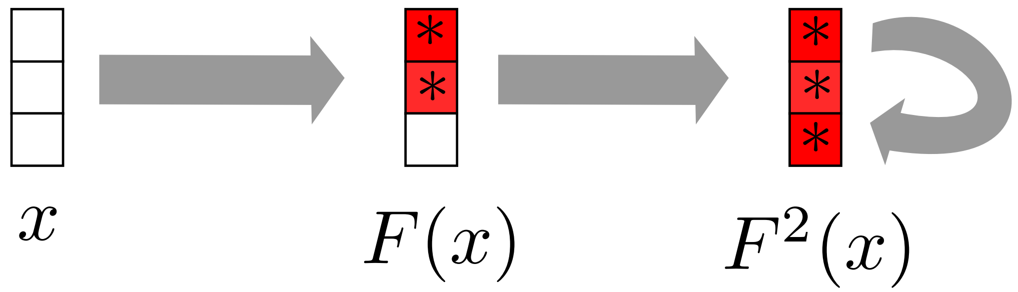

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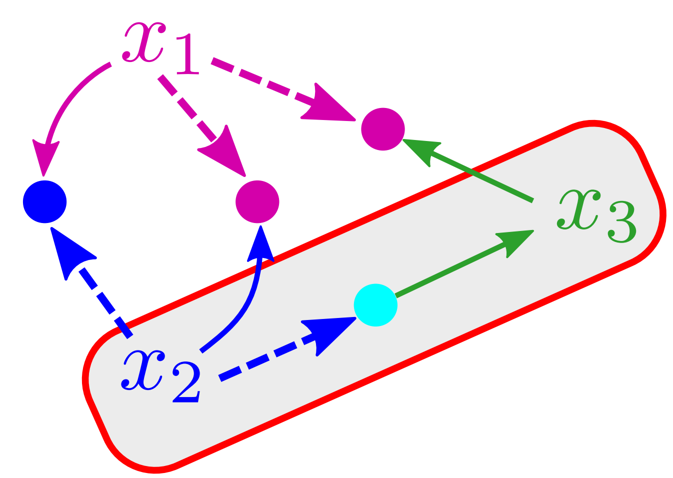

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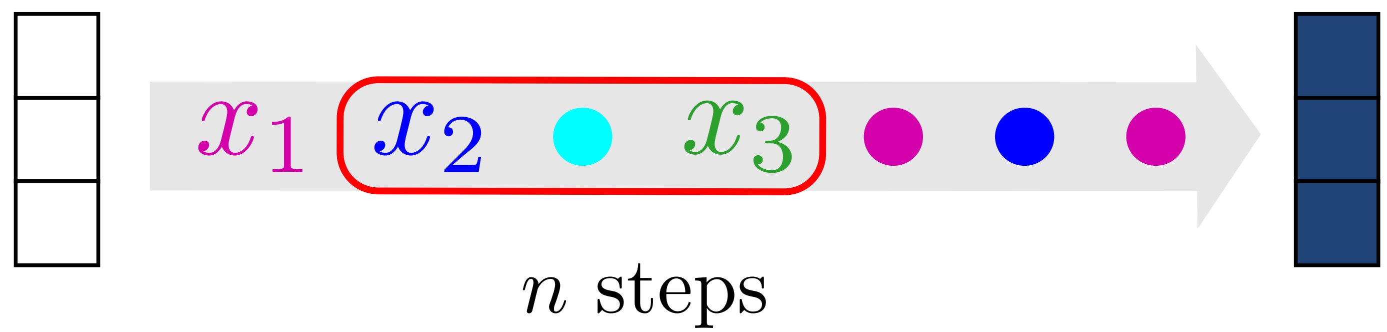
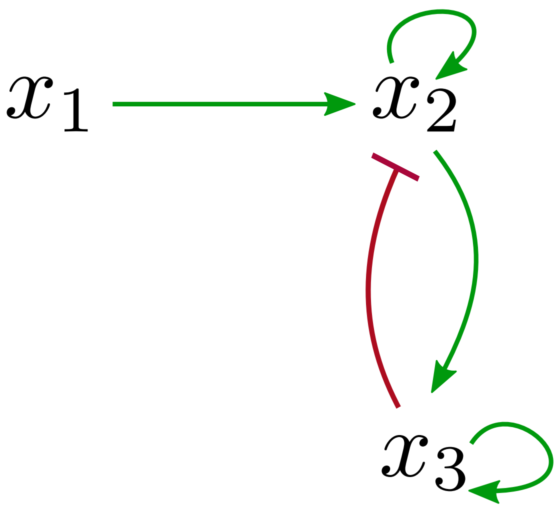
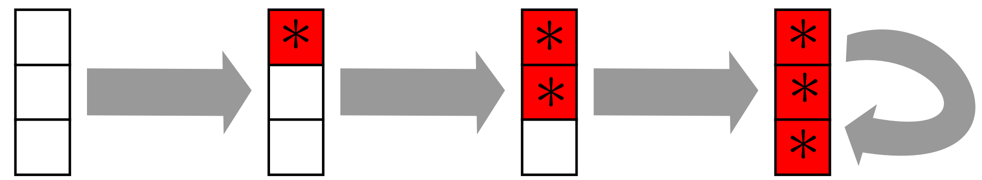
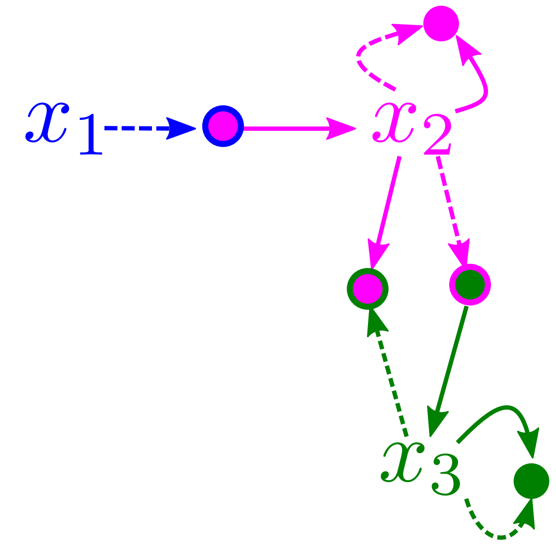


The minimal hypercube enclosing an attractor is a stable pattern

Reaching stable patterns

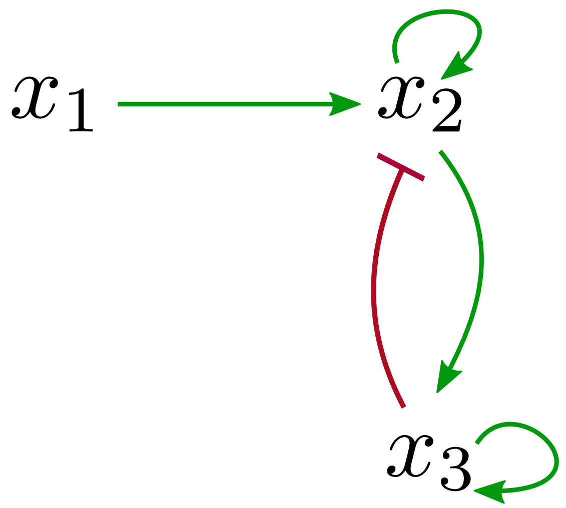


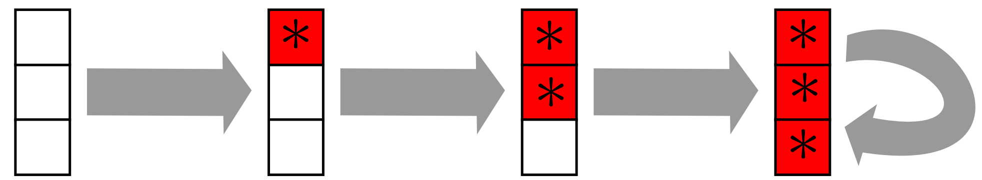


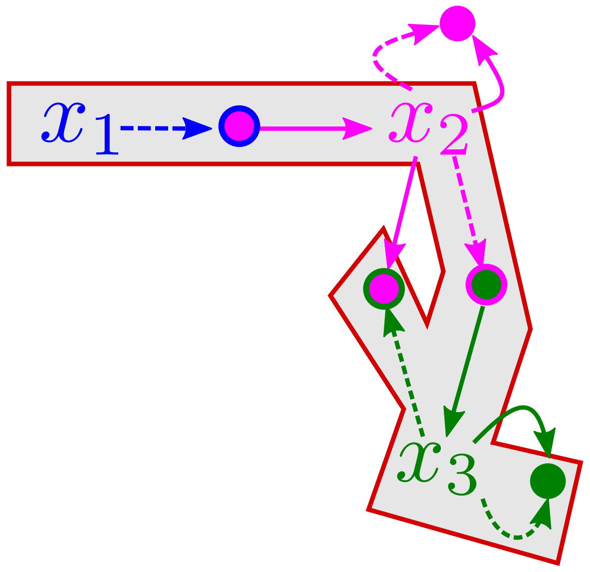


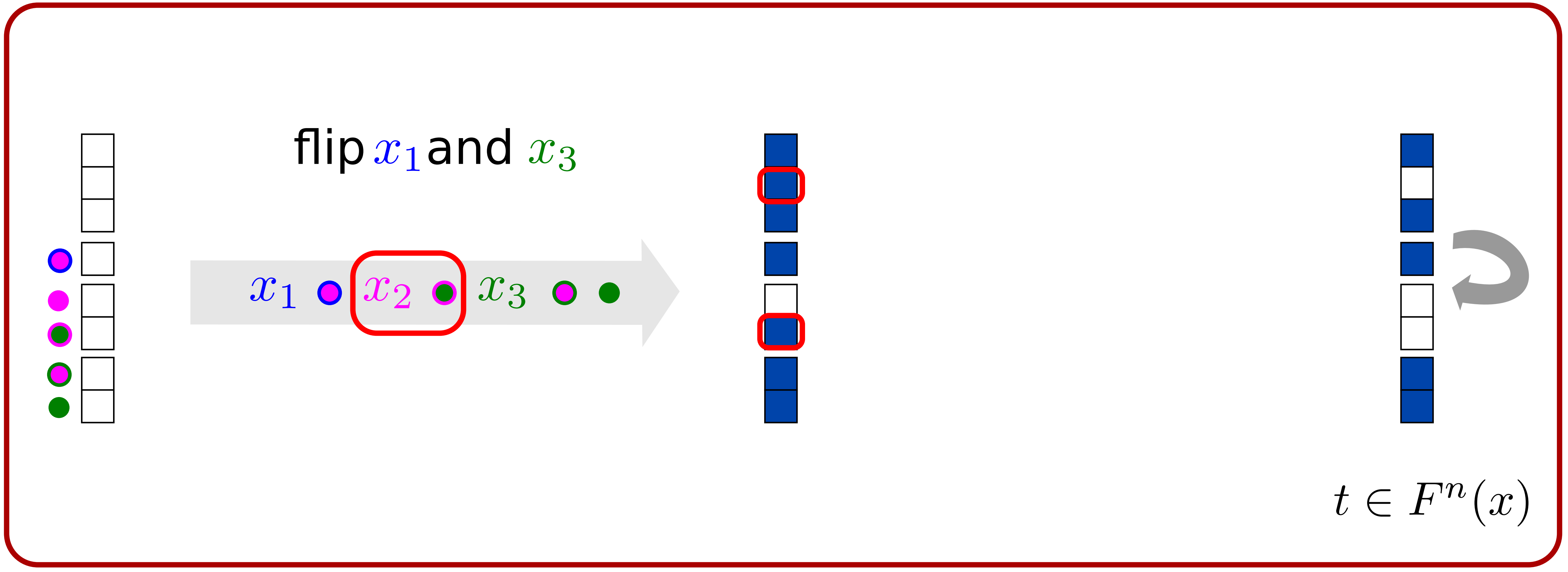
$t \in F^n(x)$

Reaching stable patterns

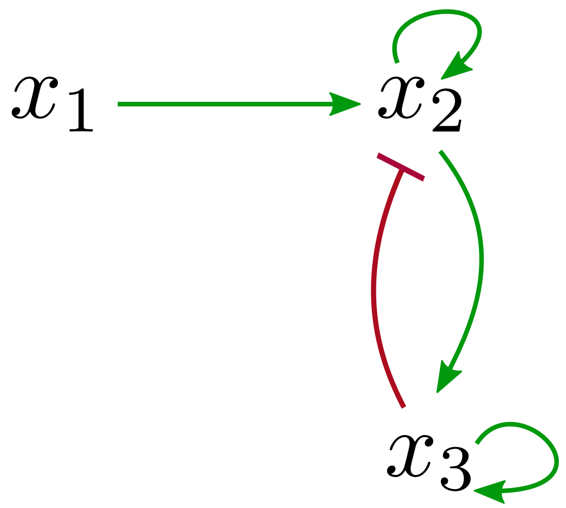


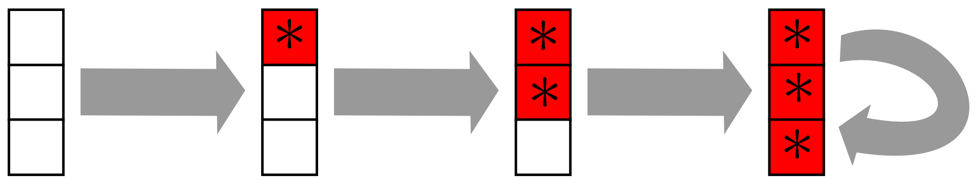


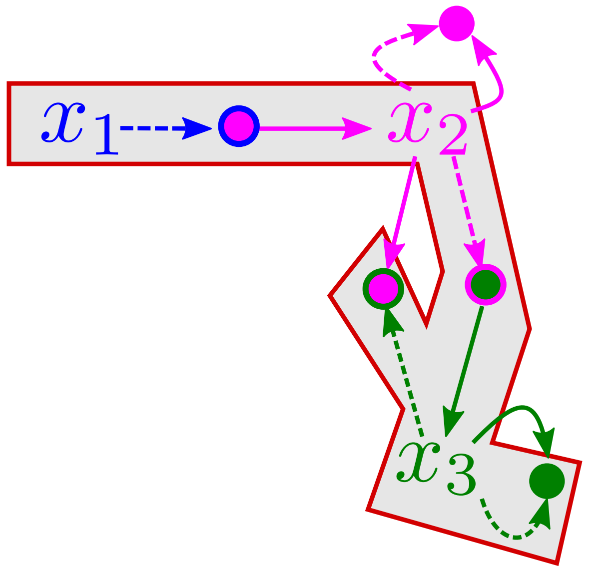


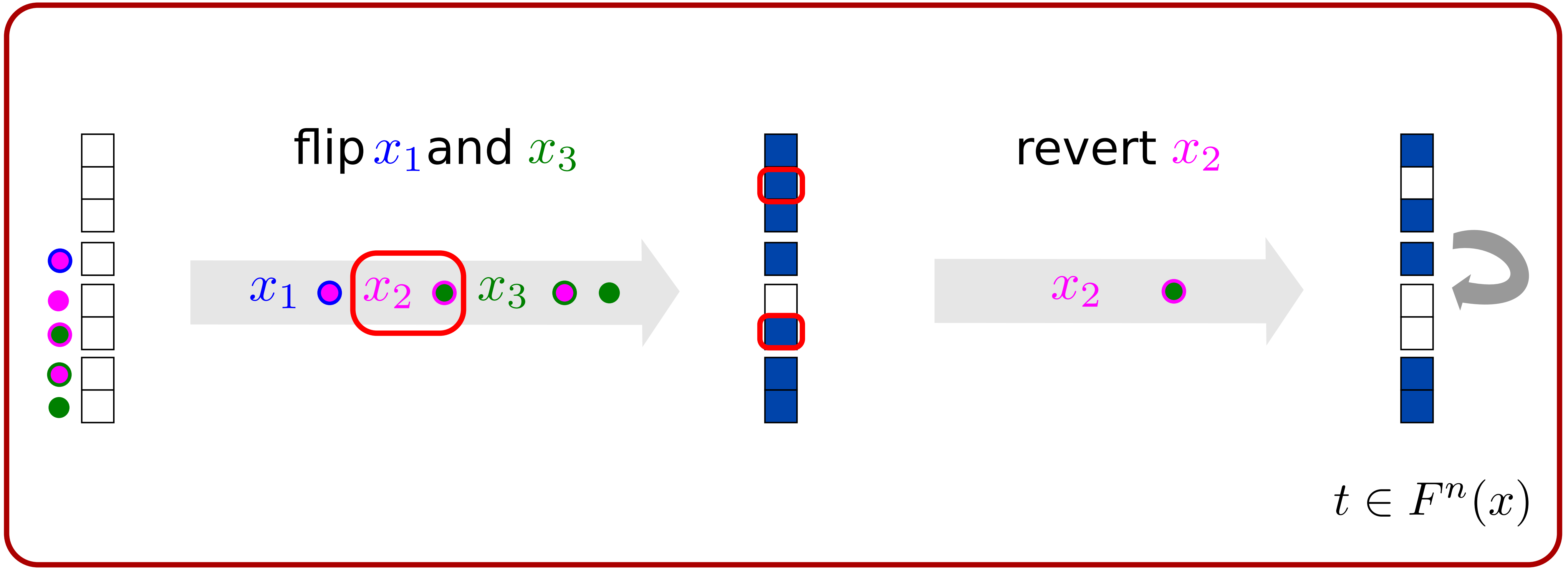


Reaching stable patterns

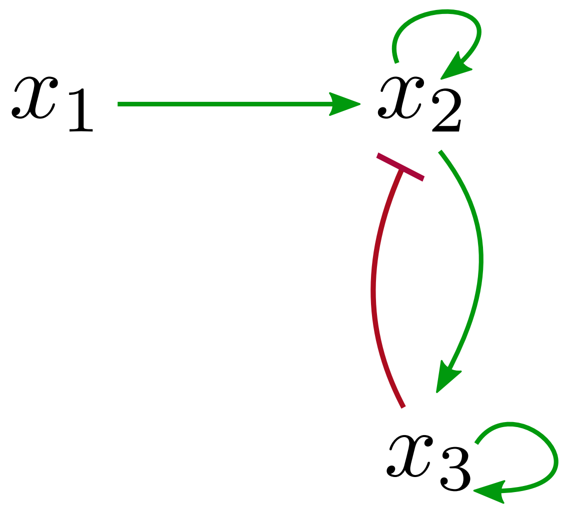


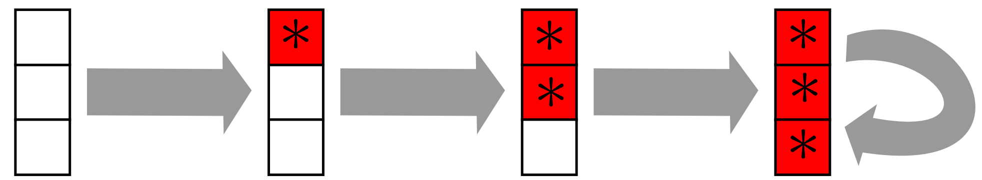


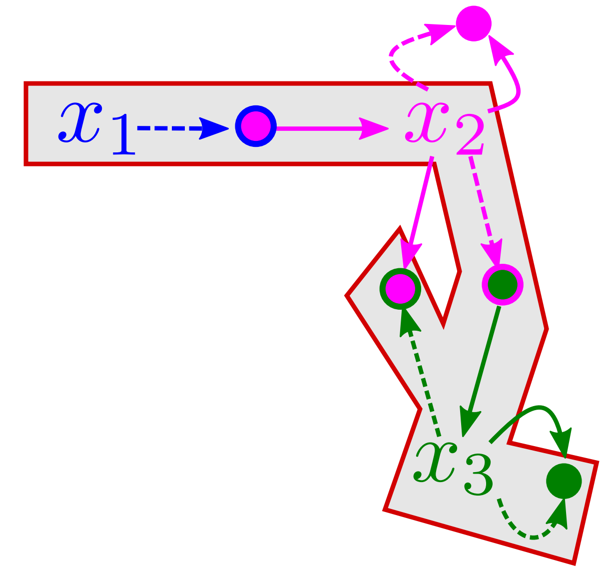




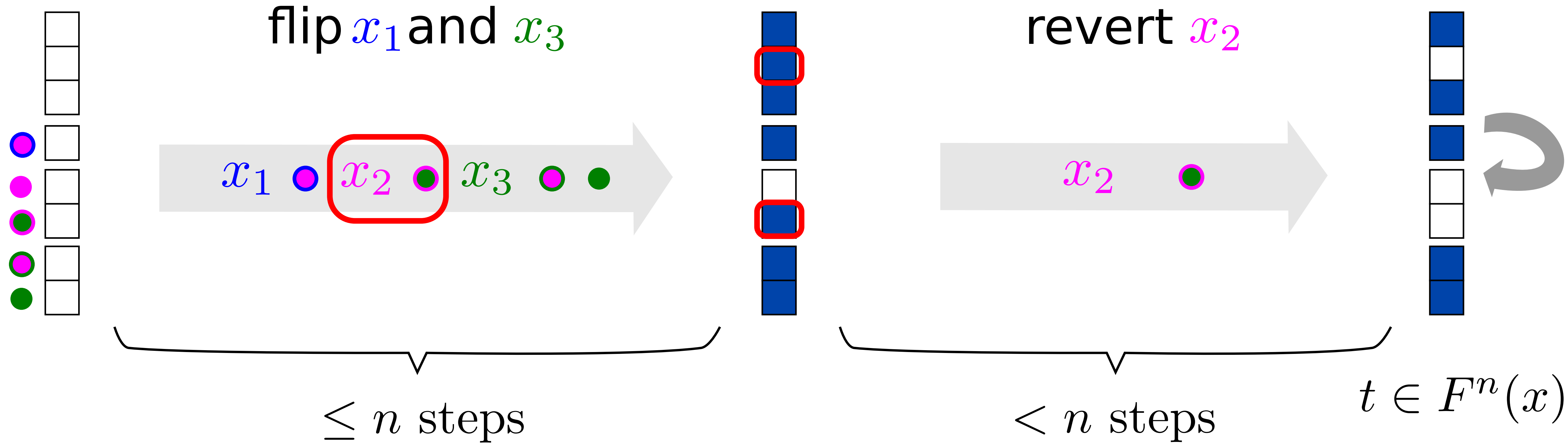
Reaching stable patterns



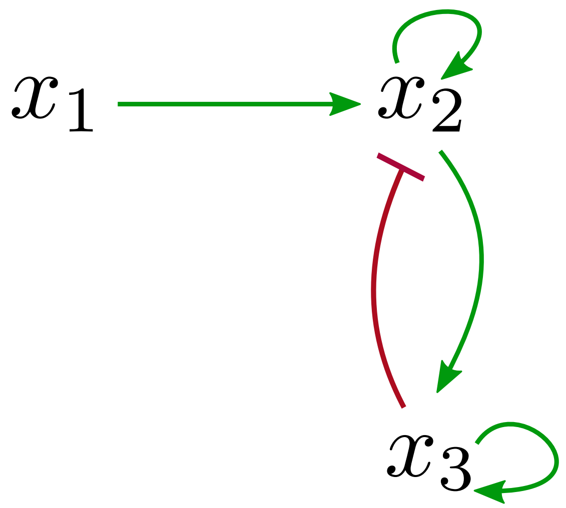


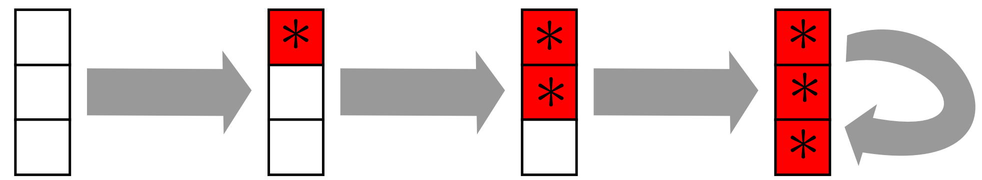


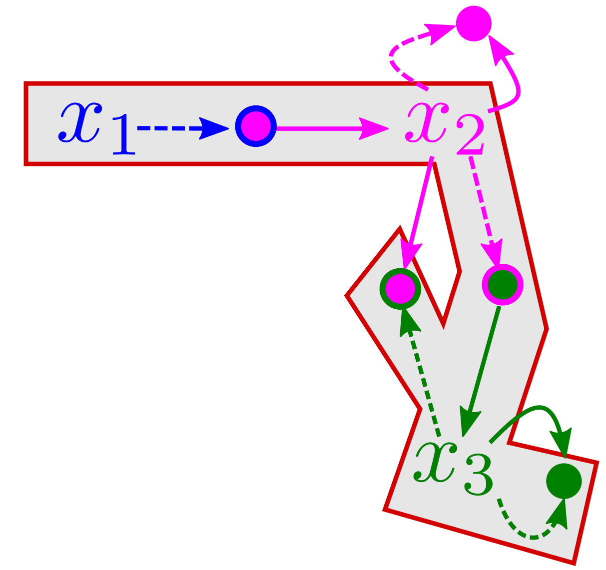
All enclosed stable patterns can be reached



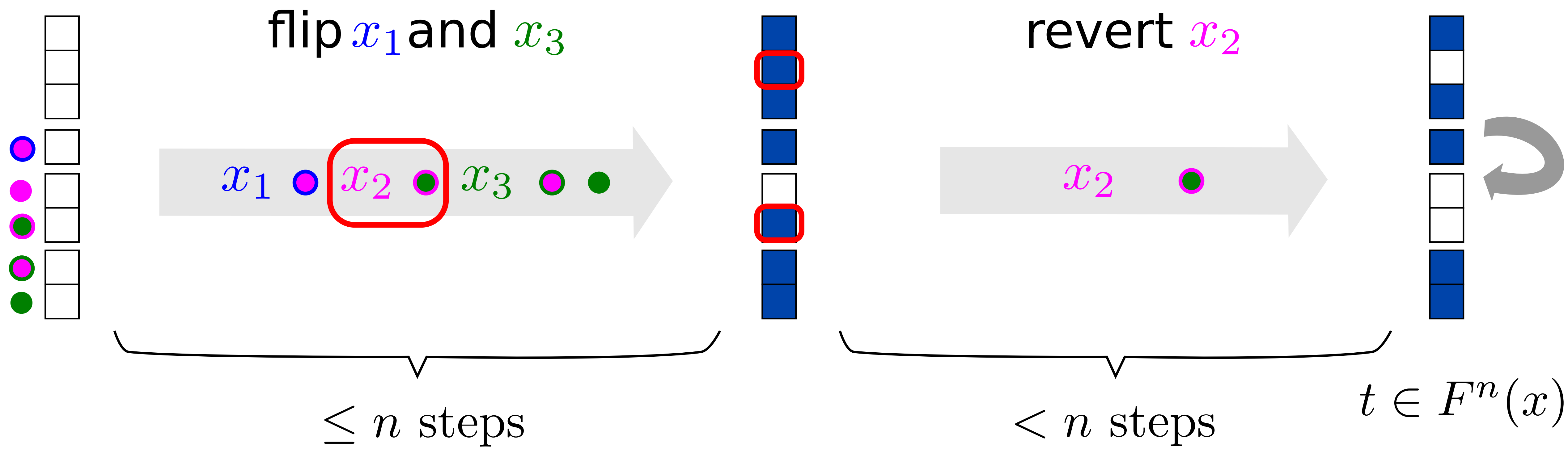
Reaching stable patterns







All enclosed stable patterns can be reached



All attractors are in terminal stable patterns

1 attractor ⇔ 1 trapspace

The minimal enclosing hypercube is a stable pattern

All attractors are in terminal stable patterns

Attractor reachable from all states in the hypercube

Attractor

⇕

stable pattern

Stable patterns are good estimators for attractors

Summary

	Async	**Buffer**	**MP**
Trapspace vs attractor	lower bound	1:1	Exact
Reach. states	2^n	???	$3n$
Reach. trapspace	2^n	$2(n+m)$	$3n$

Stable patterns as robust abstraction for attractors and reachability

Analysis directly on un-buffered model

Discussion

Limits

Assumption: variable threshold order

⬈ kinetic information → ⬊ alternative trajectories

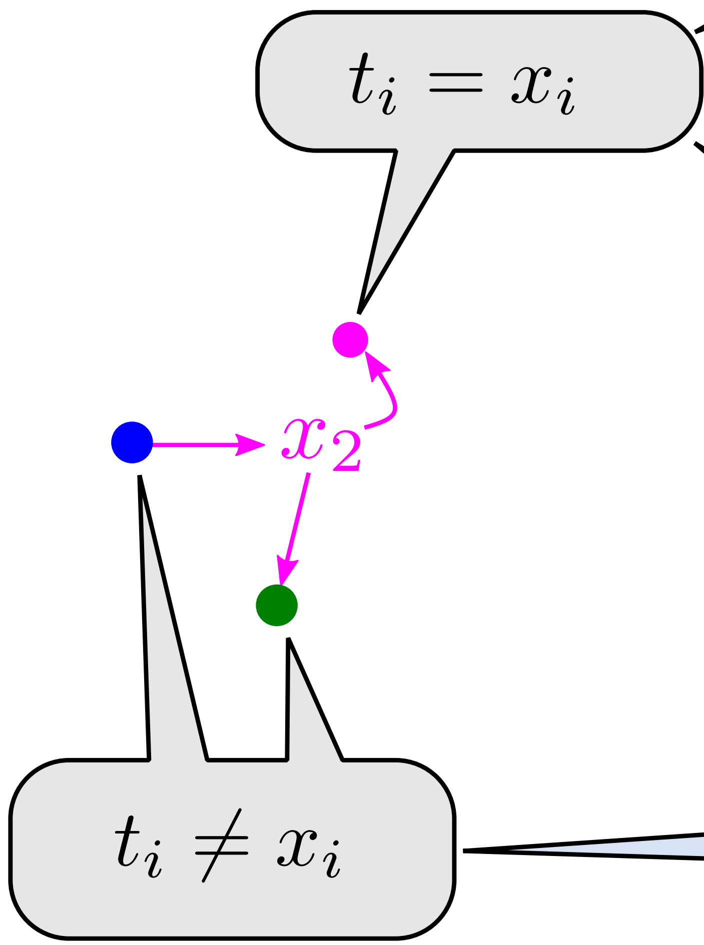
Perspectives

From partial order to constraints on kinetic parameters
Prime implicant graph to improve partial order

Can use existing stochastic tools (MaBoSS)
Derive analytic estimation of probabilities

Reverting to reach a trapspace

For each core: fix regulators to the trapspace value

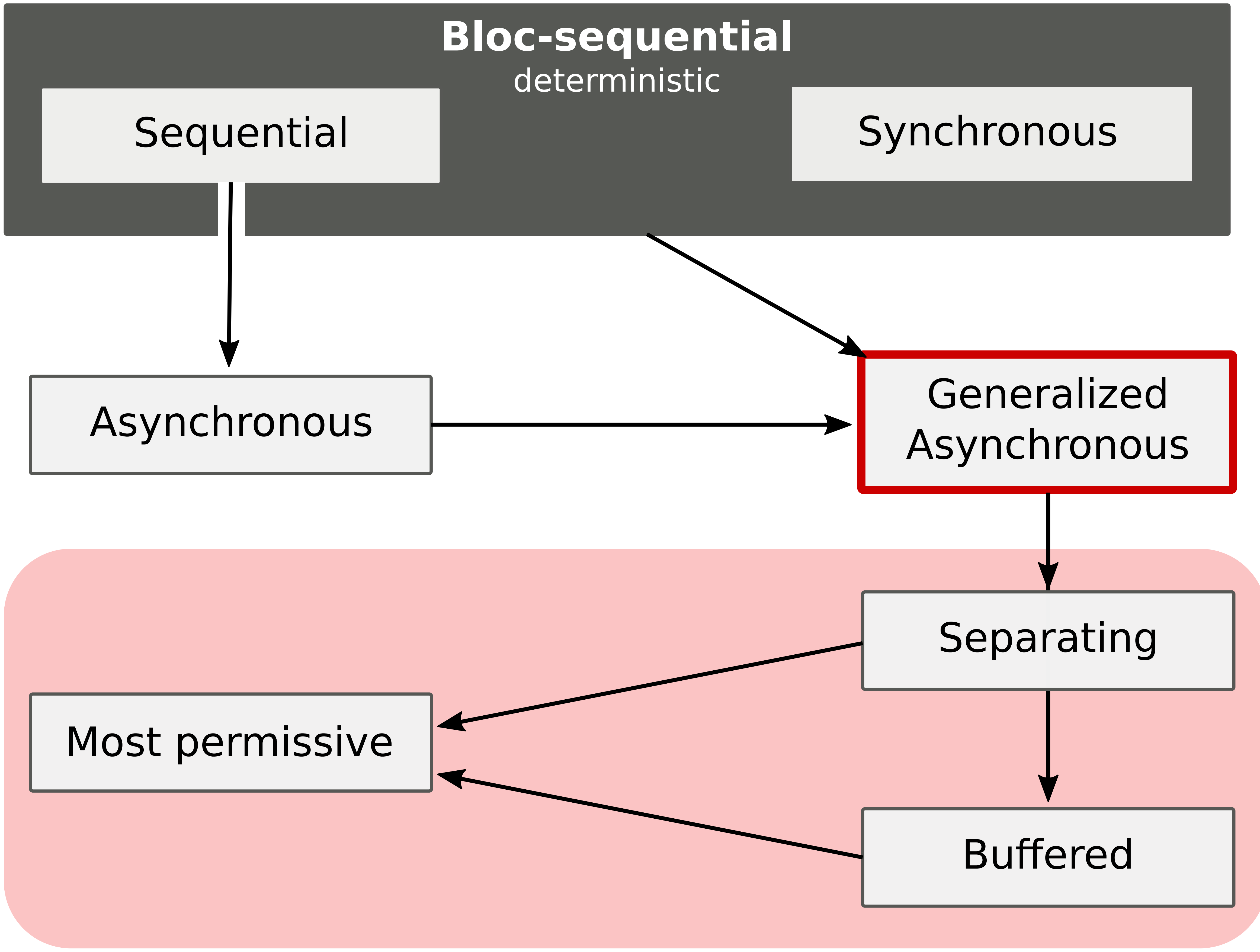


After ➜ unchanged
No other target (separating)

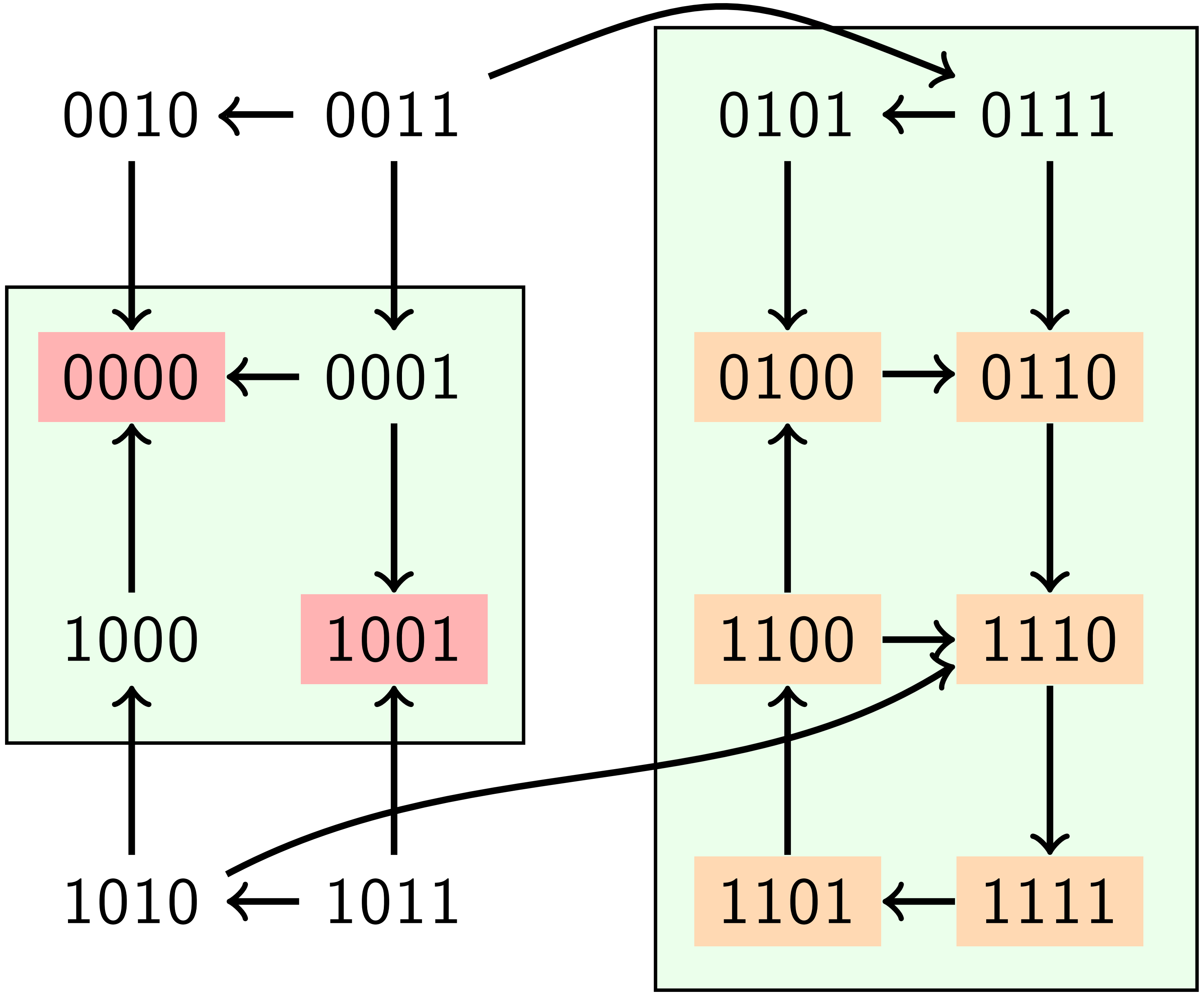
Before ➜ Revert in the order of the first step

Given by the first step

Reachability across updating semantics



Attractors = stable phenotypes



Trap spaces
(stable patterns/hypercubes)

hypercube h:
$\forall x \in h : f(x) \in h$

Constraint solving

Zanudo et al., 2013
Klarner et al., 2014

Stable states (fixed points)

state x: $f(x) = x$

Constraint solving

Naldi et al., 2007

Complex attractors

states C: $\{x : F(x) = C\}$

Symbolic exploration

Garg et al., 2008